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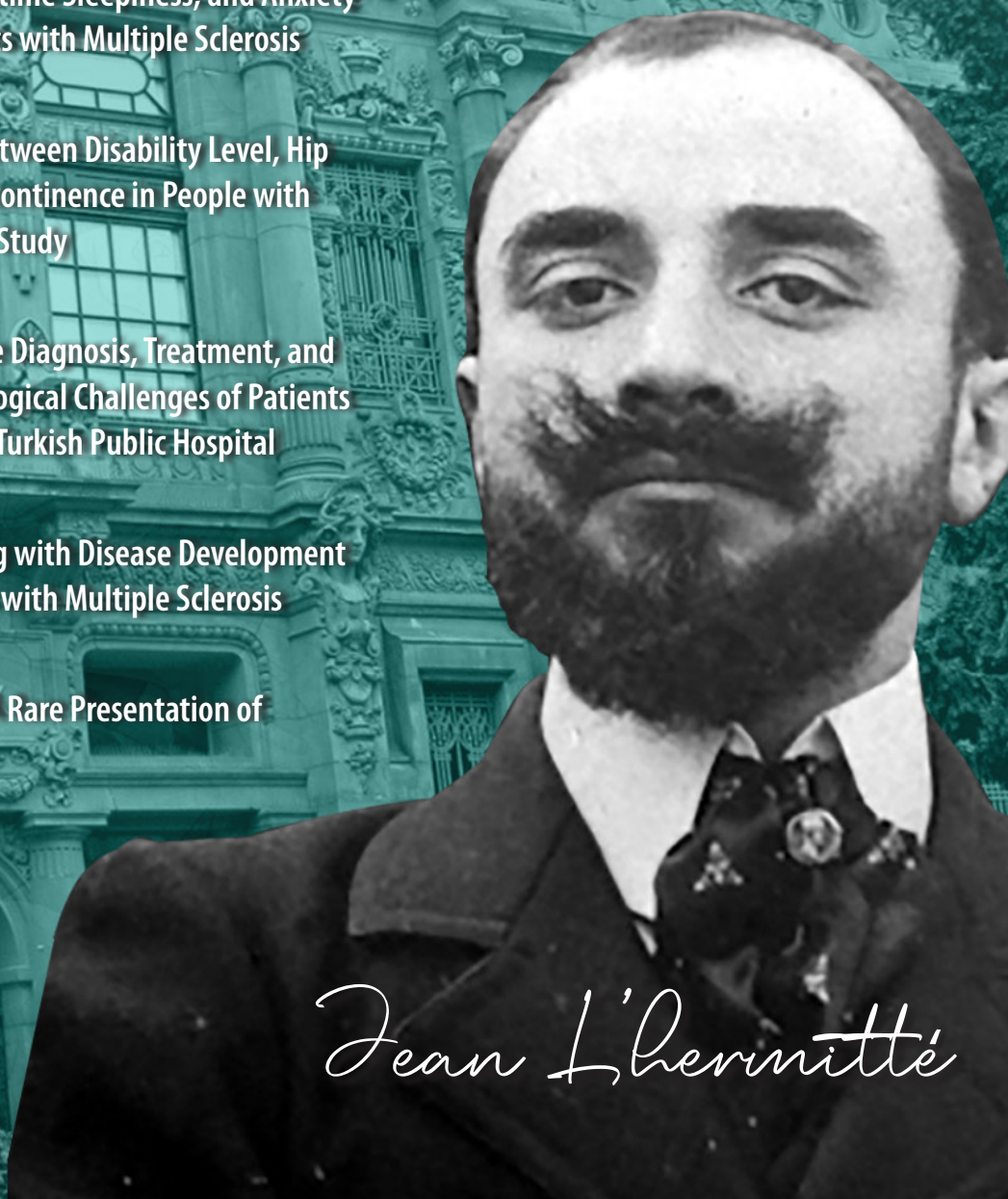

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CONTENTS

RESEARCH ARTICLES

CASE REPORT

INDEX

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RESEARCH ARTICLE

Treatment Satisfaction of Patients Using Dimethyl Fumarate for Multiple Sclerosis: A Survey Study

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Abstract

Objective: Multiple sclerosis (MS) is a chronic and progressive disease that affects the central nervous system. Dimethyl fumarate (DMF) is commonly used in the treatment of MS. This study examines the relationship between treatment adherence and quality of life (QoL) in patients undergoing DMF treatment.

Materials and Methods: The study included 227 patients using DMF. Demographic information, DMF usage duration, disease duration, and treatment adherence were obtained through surveys. Data were analyzed using the Statistical Package for the Social Sciences program. The effects of factors such as age, sex, disease duration, and treatment methods on treatment adherence and QoL were evaluated.

Results: Patients who had high adherence to DMF treatment had higher QoL. Moreover, younger patients adapted to the treatment more easily and had higher QoL. Female patients had higher treatment adherence than male patients. Additionally, treatment methods had varying effects on QoL.

Conclusion: DMF is an effective treatment for MS. The study results indicate that adherence to DMF treatment positively impacts patients' QoL and that increasing this adherence is crucial. Future studies should compare different treatment methods and comprehensively examine patients' experiences during the treatment process. Psychosocial support and education programs should be developed to enhance treatment adherence.

Keywords: Dimethyl fumarate, multiple sclerosis, treatment adherence, quality of life, demographic and clinical factors

Introduction

Multiple sclerosis (MS) is a chronic, inflammatory disease affecting the central nervous system and is often seen in young adults (1). It is characterized by widespread demyelination and axonal loss throughout the central nervous system, leading to various neurological symptoms and functional impairments. MS treatment aims to slow disease progression, manage symptoms, and improve patients' quality of life (QoL).

Dimethyl fumarate (DMF) is an oral medication used to treat MS (2). DMF has anti-inflammatory and immunomodulatory properties and induces neuroprotective effects by protecting neurons from oxidative stress. However, the effectiveness of DMF is largely dependent on treatment adherence (3), which is defined as the degree to which patients follow their treatment plan and plays a critical role in MS management.

Existing literature shows that improving treatment adherence can significantly enhance the QoL of patients with MS (4). Treatment adherence can be influenced by various demographic and clinical factors, such as age, sex, disease duration, and treatment methods (5). This study aimed to evaluate the demographic and clinical characteristics of patients undergoing DMF treatment and analyze the relationship between treatment adherence and QoL.

The findings of the study may be beneficial in developing strategies that enhance the effectiveness of DMF treatment and improve patients' QoL. In 2015, Some studies emphasized the efficacy of DMF in patients with relapsing-remitting multiple sclerosis (RRMS) and highlighted the importance of conducting comparative studies with other treatment methods such as interferon beta and glatiramer acetate (6,7).

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The present study assessed the effectiveness of and patient adherence to DMF compared with these treatment methods. In addition, this study emphasizes the importance of adherence to DMF treatment and presents the support mechanisms to improve adherence. The current study hypothesized that patients with MS and high adherence to DMF treatment have higher QoL. To test this hypothesis, the effects of demographic and clinical characteristics on treatment adherence and QoL were analyzed.

Materials and Methods

Study Design

A cross-sectional research design was used to examine the relationship between treatment adherence and QoL in patients with MS undergoing DMF.

Participants

The study included 227 patients followed at the MS clinic of University of Health Sciences Turkey, Sancaktepe Sehit Prof. Dr. Ilhan Varank Training and Research Hospital. All patients were diagnosed with RRMS according to the McDonald criteria (1). The inclusion criteria required that participants had been on DMF treatment for at least 6 months. The sample size represented 80% of the total number of patients followed in the MS clinic. The participants were aged 18-55 years, and the sample exhibited diversity in demographic variables such as age, sex, and disease duration.

The patients were examined in two separate ways according to their medication usage: The initiation treatment group, which included naive patients who started their treatment with DMF, and the switch group, comprising patients who had previously undergone other treatment protocols and later transitioned to DMF treatment (Figure 1). Additionally, the transition treatment group showed the initial treatments of the patients in the switch group (Figure 2).

Materials

The study was approved by the University of Health Sciences Turkey, Sancaktepe Sehit Prof. Dr. Ilhan Varank Training and Research Hospital Ethics Committee (number: E-46059653-050.99-215847885, date: 17.05.2023) and conducted according to the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from the participants after providing information about the study.

Data were collected during routine clinical visits of the patients. Participants were informed about the study and gave their written consent. Surveys were performed through face-to-face interviews or electronic forms. Confidentiality and privacy of the data and participants were ensured. The tools used in data collection were as follows.

Demographic Information Form

This form was used to obtain demographic information of the participants, such as age, sex, education level, marital status, and disease duration.

Multiple Sclerosis Treatment Adherence Questionnaire

The Multiple Sclerosis Treatment Adherence Questionnaire (MS-TAQ) was developed by Barber. Its Turkish validity and reliability study was conducted by Yeşilbalkan et al. (8) in 2019

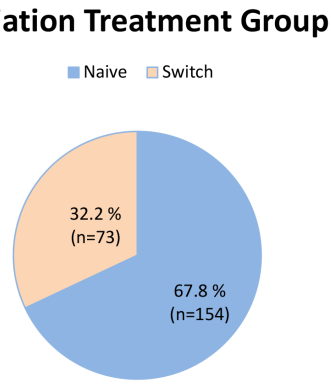

Figure 1. Distribution of naive and switch patients undergoing DMF treatment

The initial treatments of patients with multiple sclerosis who are either treatment-naïve or have switched to DMF from other therapies are shown. The initiation treatment group includes patients who started their treatment with DMF, whereas the switch group comprises patients who transitioned to DMF after previously undergoing other treatment protocols

DMF: Dimethyl fumarate

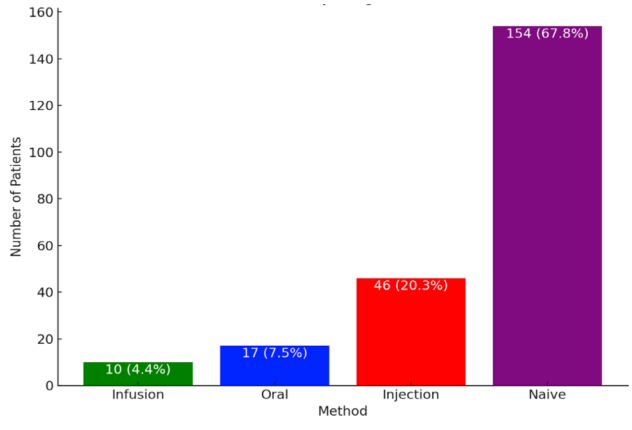

Figure 2. Initial treatments of patients in the switch group undergoing DMF treatment

The initial treatments received by patients with MS in the switch group before they transitioned to DMF are presented. It shows the distribution of patients who initially received injection, oral, or infusion therapies, providing insight into the treatment history and preferences prior to switching to DMF. The naive group represents patients who started treatment directly with DMF

DMF: Dimethyl fumarate, MS: Multiple sclerosis

The Cronbach's alpha internal consistency coefficient of the scale was 0.82. The MS-TAQ is a 5-point Likert-type scale used to determine the treatment adherence levels of individuals. High scores on the scale indicate high treatment adherence and greater attention to the treatment process.

Treatment Adherence Form

This form was used to evaluate the DMF treatment adherence levels of the participants through subjective questions. The questions measure whether patients take their medications as prescribed and how adherent they are to the treatment.

Short Form-36 Health Survey

This scale was used to assess the QoL and general health status of the patients. The Short Form-36 Health Survey (SF-36) was developed by Ware and Sherbourne (9) in 1987, and its Turkish validity and reliability study was conducted by Bilir Kaya and İçağasıoğlu (10) in 2018. The SF-36 is a 36-question self-assessment scale and measures eight dimensions: Physical function, social function, physical role difficulty, emotional role difficulty, mental health, energy/vitality, pain, and general health perception. Scores range from 0 to 100, with higher scores indicating better health status.

Statistical Analysis

Collected data were analyzed using the Statistical Package for the Social Sciences version 25.0 software. Descriptive statistics, such as frequency, percentage, mean, and standard deviation, were used to determine the distribution of demographic and clinical variables. Chi-square analysis was applied to investigate the relationship between DMF treatment adherence and QoL. Analyses examined the relationships between disease duration, sex, age, and initiation treatment group and transition treatment group variables and patients' physical activity, mental problems, experiences of side effects and body pain in the last 4 weeks, side-effect tolerance, treatment satisfaction, overall drug satisfaction, general health perception, social activity, drug use satisfaction, and overall QoL. Table 1 presents the demographic distribution of the participants, as well as disease duration, initial treatment, and DMF usage duration. The distribution of participants by treatment stage is shown in Table 2. Additionally, the chi-square analysis on the relationships between disease duration, sex, age, and the initiation and transition treatment groups with health and QoL variables is presented in Table 3.

Results

Disease Duration Analyses

Disease duration analyses revealed significant relationships between disease duration and drug satisfaction (χ^2=0.007) and overall QoL (χ^2=0.050). These findings indicate that disease duration has a significant impact on these variables. Detailed analyses showed that participants with a disease duration of >5 years had higher levels of drug satisfaction compared to those with a disease duration of ≤5 years (mean satisfaction score: 72.5±8.3 vs. 58.9±7.2; p=0.007). This shows that long-term patients are more satisfied with their treatments. Regarding overall QoL, participants with a disease duration of >5 years had a lower overall QoL compared to those with a disease duration of ≤5 years (mean QoL score: 48.2±10.1 vs. 63.4±9.7; p=0.050). This finding indicates that disease duration negatively impacts overall QoL. Thus, the disease duration variable induces significant differences in drug satisfaction and overall QoL. While long-term patients show more positive results in drug satisfaction, they show more negative results in overall QoL. These findings demonstrate that disease duration critically affects health and QoL. No significant relationships were found between disease duration and other variables.

Sex Analyses

According to the results, significant relationships were found between sex and physical activity (χ^2=0.022), general health perception (χ^2=0.028), overall QoL (χ^2=0.041), and body pain in the last month (χ^2=0.005). These reveal that sex has a significant impact on these variables. Detailed analyses showed that females were more successful than males regarding physical activity levels (mean physical activity score: 42.3±6.1 for females vs. 35.2±5.7 for males; p=0.022). As regards general health perception, females rated themselves as healthier compared to males (mean scores: 7.1±1.5 vs. 5.8±1.8; p=0.028), and females scored higher in overall QoL compared to males (mean QoL score: 66.4±8.9 vs. 51.2±9.3; p=0.041). Additionally, females reported less body pain in the last month compared to males (median pain scores: 2 vs. 4; p=0.005). Therefore, female participants showed more positive results in physical activity, general health perception, and overall QoL and experienced less body pain in the last month compared to male participants.

Age Group Analyses

In the age group analyses, significant relationships were noted between age and mental problems (χ^2=0.011) and overall QoL (χ^2=0.024). These findings show that age has a significant impact on these variables. A significant relationship was found between age group and mental problems (mean mental problems score: 62.0±8.2 for ≤29 vs. 45.5±7.4 for 30-40 and 50.3±8.1 for >40; p=0.011). This shows that the ≤29 age group experienced more mental problems compared to the older age groups. Regarding overall QoL, the 30-40 age group reported the highest QoL (mean score: 72.1±9.4) compared to the ≤29 (mean score: 60.5±8.7) and >40 (mean score: 55.8±9.0) (p=0.024) age groups. Therefore, the age group variable caused significant differences in mental problems and overall QoL. Younger participants experienced more mental problems, whereas participants in the 30-40 age group showed more positive results in overall QoL.

Initiation Treatment Group Analyses

In the present study, the results from the analyses of patients who had previously undergone another treatment and continued their treatment with DMF showed a significant relationship only between the initiation treatment group and treatment interruption variable (χ^2=0.004). This finding indicates that patients who had previously undergone another treatment and are currently using DMF more possibly interrupt their treatment compared to those who started their treatment with DMF (percentage of treatment interruption: 32% in the switch group vs. 10% in the naive group; p=0.004).

Transition Treatment Group

In the transition treatment group analysis, patients who had previously received injection, oral, and infusion treatments were compared with naive patients who started treatment directly with DMF. The chi-square test showed significant relationships between the transition treatment group and general health perception (χ^2=0.009) and body pain in the last month (χ^2=0.039). These show that patients who started their treatment with DMF had distinct differences in general health perception and body pain experiences. Specifically, patients who started treatment with DMF had a more positive general health perception (mean scores: 78.5±7.6 for injection, 65.3±6.9 for infusion, and 52.8±7.0 for oral; p=0.009) and reported less body pain in the last month (median pain scores: 1 for injection, 3 for infusion, and 5 for oral; p=0.039). Hence, different drug usages (initiation and transition treatment groups) caused significant differences in certain health and QoL variables.

Linear Regression Analysis

Linear regression analysis was performed to examine the factors affecting overall QoL. First, based on the Pearson correlation analysis, significant relationships were found between social activity (r=-0.42, p<0.05) and general health perception (r=1.03, p<0.05) and overall QoL. According to the regression model, social activity alone explained 21.3% of the variance in overall QoL (R^2=0.213, adjusted R^2=0.209). A decrease in social activity was significantly associated with a decline in overall QoL (coefficient: -0.4199, p=0.000). When general health perception was added to the model, it explained 42.6% of the variance in overall QoL (R^2=0.426, adjusted R^2=0.421), with an increase in general health perception significantly associated with an improvement in overall QoL (coefficient: 1.0293, p=0.000). Other variables such as sex, age, disease duration, medication satisfaction, physical activity, and mental health problems were not statistically significant in this model. These results are presented in Table 4.

Another linear regression analysis was performed to assess the explanatory power of sex, age, disease duration, medication satisfaction, physical activity, and mental health problems on general health perception. Pearson's correlation analysis indicated that physical activity (r=0.457, p<0.05) and mental health problems (r=-0.358, p<0.05) were moderately correlated with general health perception. As physical activity increased, general health perception significantly improved, whereas an increase in mental health problems was associated with a decline in general health perception. The regression model explained 27.4% of the variance in general health perception (R^2=0.274, adjusted R^2=0.251), with the highest explanatory power attributed to physical activity and mental health problems. These findings also are detailed in Table 4.

Discussion

This study examined the effects of DMF treatment on treatment adherence and QoL in patients with MS and presented significant findings. The results are consistent with those in the existing literature, supporting the positive effects of DMF treatment adherence on QoL. A study by Gold et al. (11) indicated that younger patients adapted to treatment more easily and had higher QoL, which aligns with our findings.

In this study, patients with high adherence to DMF treatment were found to have higher QoL. Similarly, some studies suggest that medication adherence positively affects QoL in MS treatment (12,13). Considering the side effects of DMF and the adaptation process of patients to the treatment, it is understood that treatment adherence directly impacts treatment outcomes. This aligns with the findings of a study by Nieto González et al. (14), wherein the nasal application of DMF was explored to reduce side effects, which could further

Table 1. Demographic characteristics of all participants

Demographic feature	Value
Average age (years)	33.08
Age range (years)	18-55
Average disease duration (years)	6.43
Average DMF usage duration (months)	16.74
Female (n, %)	180 (79.3%)
Total participants (n)	227

DMF: Dimethyl fumarate

Table 2. Distribution of participants by treatment stage

Treatment stage	Injection (n, %)	Oral (n, %)	Infusion (n, %)	Naive (n, %)
Initiation treatment (naive)	-	-	-	154 (67.8%)
Transition treatment (switch)	46 (20.3%)	17 (7.5%)	10 (4.4%)	-
Total patients (n, %)	46 (20.3%)	17 (7.5%)	10 (4.4%)	154 (67.8%)

Table 3. Chi-square analysis results of the relationships between disease duration, sex, age group, initiation treatment group, and transition treatment group with health and quality of life variables

Variable	Comparison	Values	p-value
Disease duration	>5 years vs. ≤5 years	Satisfaction: 72.5±8.3 vs. 58.9±7.2 QoL: 48.2±10.1 vs. 63.4±9.7	0.050
Sex	Female vs. male	Physical activity: 42.3±6.1 vs. 35.2±5.7 Health perception: 7.1±1.5 vs. 5.8±1	0.022*
Age group	≤29 years vs. 30-40 years vs. >40 years	Mental problems: 62.0±8.2 vs. 45.5±7.4 vs. 50.3±8.1 QoL: 72.1±9.4 vs. 60.5±8.7	0.011*
Initiation treatment group	Naive vs. switch	Treatment interruption: 32% vs. 10%	0.004*
Transition treatment group	Oral vs. infusion vs. injection	Health perception: 78.5±7.6 vs. 65.3±6.9 vs. 52.8±7.0 Pain: 1 vs. 3 vs. 5	0.009*

Note: The symbol (*) indicates statistical significance (p≤0.05).

QoL: Quality of life

Table 4. Regression results for quality of life and general health perception

Model variables	R^2	Adjusted R^2	Coefficient	p-value
Social activity	0.213	0.209	-0.4199	0.0*
General health perception	0.436	0.421	1.0293	0.0*
Physical activity	0.274	0.251	0.457	0.05*
Mental health problems	0.274	0.251	-0.358	0.05*

Note: The symbol (*) indicates statistical significance (p≤0.05).

support treatment adherence. This novel approach highlights the need for personalized DMF administration methods to improve patient comfort and adherence outcomes.

In this study, demographic and clinical factors such as age, sex, and disease duration were found to be determinants of treatment adherence and QoL. The finding that younger patients adapted to treatment more easily and had higher QoL is consistent with the results of other studies (15). Additionally, the higher treatment adherence of female patients compared to male patients supports findings in the literature regarding sex differences (16).

The different impacts of DMF administration methods (e.g., injection, oral, and infusion) on QoL highlight the psychological and physical burden of treatment methods on patients. A study on the impact of treatment methods on patients' QoL revealed that injection treatments cause more stress and discomfort in patients, whereas oral treatment methods provide higher patient satisfaction (17).

In the current study, a significant portion of patients experienced side effects related to DMF treatment; however, their overall satisfaction was high. This indicates that the balance between the effectiveness and side effects of DMF is tolerable for patients. Furthermore, the study by Gold et al. (18) in 2017 also reported that the side effects of DMF treatment were manageable, and overall patient satisfaction was high. This is consistent with the findings of Jožef et al. (19) in 2024, which highlighted the influence of mental health on DMF adherence and QoL in patients with MS. It showed that mental health status, including levels of depression and anxiety, directly influences treatment adherence and satisfaction with DMF.

The findings of this study reveal that increasing treatment adherence in DMF treatment can improve the QoL of patients. Future studies should include comparative analyses of different treatment methods and a more detailed examination of patients' experiences during the treatment process. Additionally, the development of psychosocial support and education programs to enhance treatment adherence is recommended.

Moreover, in the current study, it was found that social activity and general health perception had significant relationships with overall QoL. These findings are consistent with those in the existing literature, which emphasize the crucial impact of social and health perceptions on the QoL of patients with MS. Particularly, physical activity was widely acknowledged as a key factor in improving physical functioning and mental health, which in turn leads to higher QoL for patients with MS (20,21). However, our study did not find a direct significant relationship between physical activity and QoL, which contrasts with some findings in the literature (22). This discrepancy may be due to differences in disease severity or physical activity levels within our sample. For example, patients with higher levels of disability may face difficulties in participating in regular physical activity, which could reduce its impact on QoL (23).

Similarly, mental health issues such as depression and anxiety were not found to be directly related to QoL. In contrast, several studies emphasized that mental health is a key determinant of QoL in patients with MS (24). This could be attributed to the homogeneity of the mental health status within our sample or the influence of mediating factors including social support. Furthermore, as demonstrated in a 2023 study by Moccia et al. (25), consistent physical activity was found to have a positive impact on physical and mental well-being among DMF-treated patients with MS, underscoring the importance of promoting physical activity within this patient group.

In our study, sex, age, and disease duration did not show significant relationships with QoL. However, the literature shows that women and younger patients typically report higher QoL (26). This inconsistency may be due to the fact that the present study did not fully account for the varying disease progression and treatment modalities.

However, significant relationships were noted between general health perception and physical activity and mental health. Various studies have reported that physical activity improves general health perception by enhancing physical functioning, such as muscle strength, balance, and mobility (27). These findings explain the stronger association between physical activity and mental health with general health perception compared with QoL. While QoL is influenced by a wide range of factors, such as social relationships and emotional state, general health perception is more closely tied to how individuals assess their physical and mental health (28).

Future Research Implications

The findings of this study highlight the positive effects of DMF treatment on adherence and QoL in patients with MS. However, future studies should consider several critical points for a more comprehensive understanding. Comparative studies directly evaluating DMF against other MS treatment methods are warranted to provide objective insights into its effectiveness and patient satisfaction relative to alternative therapies. Additionally, long-term follow-up studies are crucial to explore the sustained impact of DMF on patients' QoL and adherence over time and its long-term side effects. Furthermore, intervention studies that assess the benefits of psychosocial support and education programs designed to improve adherence to DMF should be pursued, focusing on their influence on patient outcomes. Further, investigation into how adherence to DMF and QoL vary across different demographic groups, including age, sex, socioeconomic status, and cultural backgrounds, is essential for personalizing treatment approaches. Moreover, control group studies using placebos or alternative treatments are required to objectively evaluate the efficacy and side effects of DMF. Implementing these research recommendations will deepen our understanding of DMF's role in MS treatment, enhancing patient care and optimizing treatment strategies to improve the QoL of those affected by the disease.

Study Limitations

The demographic and clinical characteristics of the 227 participants may not adequately represent the general population. Factors such as age, sex, and disease duration distribution can affect the generalizability of the results. Studies based on survey data assume that participants provide accurate and honest responses. However, factors including bias and misunderstanding can affect the results. In particular, data based on patients' self-reports may have reliability issues if not supported by objective measurements. The measurement of DMF usage duration and treatment adherence may not fully reflect long-term outcomes. Short-term side effects and long-term treatment-related variability can affect the accuracy of the results. It is possible that individuals who have discontinued the medication did not participate in the study. The present study evaluated the QoL of patients currently using the medication. The way patients experience and report side effects can be subjective, which can create variability in the evaluation of side effects and may not fully reflect the impact on treatment adherence. Comparing the effectiveness of DMF treatment and its effects on the QoL was challenging owing to the absence of a control group. Moreover, the inability to compare with placebo or other treatment methods makes it difficult to isolate treatment effects, and the cross-sectional study design makes it challenging to determine causal relationships. Not being able to identify the relationship between treatment adherence and QoL over time can overlook the dynamic nature of the results. Psychosocial factors that could affect patients' QoL (e.g., family support, socioeconomic status, and psychological support) were not detailed in this study. Ignoring these factors may not comprehensively present the results. General health status and presence of other chronic diseases can affect the effects of DMF treatment and patients' QoL. In this study, other health status variables were not adequately controlled.

DMF is considered an effective treatment option for patients with MS. The results of this study emphasize that adherence to DMF treatment positively impacts patients' QoL and that it should be increased. Consistent with the existing literature, the relationship between treatment adherence and QoL is critical for optimizing treatment processes and improving patients' QoL.

Conclusion

High adherence to DMF treatment improves the QoL of patients with MS. Younger and female patients, in particular, showed higher adherence and QoL, highlighting the importance of demographic factors. Oral DMF treatments are associated with greater patient satisfaction compared to injection methods. Despite some side

effects, overall satisfaction remains high, indicating an adequate balance between treatment efficacy and side effects.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, Sancaktepe Sehit Prof. Dr. Ilhan Varank Training and Research Hospital Ethics Committee (approval no: E-46059653-050.99-215847885, date: 17.05.2023).

Informed Consent: Written informed consent was obtained from the participants after providing information about the study.

Footnotes

Authorship Contributions

Concept: S.D., Design: M.T., Data Collection or Processing: E.H.U., I.G.D., Analysis or Interpretation: M.T., D.C.T., Literature Search: E.H.U., D.C.T., I.G.D., Writing: M.T.

Conflict of Interest: No conflict of interest was declared by the authors.

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RESEARCH ARTICLE

The Relationship Between Retinal Layer Thickness and Cognition in People with Multiple Sclerosis

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Abstract

Objective: Optical coherence tomography (OCT) and OCT-angiography (OCT-A) are non-invasive techniques for investigating retinal layers and blood flow. Axonal loss in neurodegenerative disorders like multiple sclerosis (MS) can be evaluated with OCT. The retinal nerve fiber layer (RNFL) and ganglion cell inner plexiform layer (GCIPL) are mainly affected layers by MS-related axonal loss. As a result, these layers can be a biomarker of disability, cortical volume and cognition in people with MS (pwMS). This study investigates the relationship between cognition and retinal nerve layers' thickness and retinal vessel density in pwMS.

Materials and Methods: The participants' OCT and OCT-A examinations were evaluated retrospectively. The participants with a history of bilateral optic neuritis and less than 12 years of education were excluded from the study. The participants were divided into the following two groups: pwMS with optic neuritis (ON+) and pwMS without optic neuritis (ON-). The unaffected eyes were evaluated in the ON+, and the mean values of eyes were evaluated in the ON- group. Demographic variables, Expanded Disability Status Scale (EDSS) and Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS), which include: Symbol Digit Modalities Test (SDMT), Brief Visuospatial Memory Test-Revised (BVMT-R), California Verbal Learning Test-II (CVLT-II) were examined.

Results: Twenty-eight participants were in the ON+ group, and 56 pwMS were in the ON- group. The thickness of GCIPL inferior and temporal quadrants exhibited a weak negative correlation with BVMT-R in the ON-group. The vessel density of optic disc inferior quadrant results showed a weak positive correlation with SDMT in the ON-group (ρ=0.329, p=0.02). The superonasal quadrant of RNFL had a moderate negative correlation with the results of CVLT-II in the ON+ group (ρ=-0.458, p=0.016). On the other hand, GCIPL, in all quadrants except the centrum, positively correlated with SDMT in the ON+ group. Similar correlation results were detected between the inferotemporal/global thickness of RNLF and SDMT in the ON+ group.

Conclusion: The thicknesses of specific quadrants of RNFL and GCIPL might have a weak to moderate correlation with information processing speed, particularly in ON+ pwMS. Only inferior quadrant optic disc vessel density showed a weak correlation with information processing speed in ON- group.

Keywords: Optical coherence tomography, optical coherence tomography-angiography, cognition, multiple sclerosis

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Introduction

Multiple sclerosis (MS) is primarily a demyelinating immune-mediated disorder that affects the central nervous system. Neurodegeneration and axon loss are also key pathophysiological contributors of progression and disability (1). Optical coherence tomography (OCT), which provides direct visualization of retinal layers, is an efficient method to detect axonal loss in people with MS (pwMS). Axonal degeneration in certain retinal layers can show disability accumulation and brain atrophy in pwMS with and without optic neuritis (2).

Another possible pathogenic cause of MS is central nervous system microvascular damage and hypoxia (3,4). Low cerebral blood perfusion in pwMS and low grey matter perfusion in pwMS were associated with worse cognitive skills (5). Retinal structures were derived embryonically from similar places to the central nervous system. Vascular structures and the retinal blood barrier also showed similarities with the central nervous system (6). So, the similar pathogenic mechanisms that are seen in central nervous system microvascularity can be seen in retinal vascularity. Retinal microvascular damage can be detected in pwMS and detected via OCT-angiography (OCT-A) (7-9). Although the results vary, disability accumulation may be associated with different OCT-A measurements (9-13). Further, the measurements of OCT-A might be related to grey and white matter atrophy in pwMS, and a longitudinal decrease might be associated with worsening Expanded Disability Status Scale (EDSS), brain atrophy or cognitive skills (14).

Cognitive impairment can be detected in 30-75% of pwMS. These deficits are more common in progressive MS groups (15). Axonal loss and neurodegeneration are the main factors in irreversible cognitive impairment in pwMS, and OCT can detect these conditions by measuring the retinal layers (16). Although the results were contradictory, the retinal nerve fiber layer (RNFL) correlates with the Symbol Digits Modality Test (SDMT), California Verbal Learning Test (CVLT) and Brief Visuospatial Memory Test-Revised (BVMT-R) (17,18). Also, atrophy in the RNFL can predict further cognitive impairment (19,20). Studies presented different results regarding the relationship between Ganglion cell inner plexiform layer (GCIPL) thickness and cognition (17,18). On the other hand, while research indicated that cerebral hypoperfusion may have a correlation with cognitive skills in pwMS, limited studies investigated the relationship between cognition and OCT-A results (14).

In this study, we hypothesized that retinal thickness and retinal microvascular density could be a reliable biomarker for cognitive status in relapsing-remitting MS. For this purpose, we investigated the OCT and OCT-A measurements and their relation to cognitive tests of pwMS.

Materials and Methods

This cross-sectional study was approved by the Non-invasive Research Ethics Board of Dokuz Eylul University (protocol no.: 6546-GOA, decision no.: 2021/22-03). The study included individuals with relapsing-remitting pwMS with at least one OCT/OCT-A test during their follow-up. The OCT and OCT-A results were examined retrospectively. The thicknesses of retinal layers -macular Ganglion Cell Inner Plexiform Layer (GCIPL) and peripapillary Retinal Nerve Fiber Layer (RNFL)- in different areas were studied. Global thickness, four quadrants and two regions were examined separately for RNFL (SN=Superionasal/ST=Superiotemporal/IN=Inferonasal/IT=Inferotemporal/T=Temporal/N=Nasal). The central region and quadrants were analysed independently in the context of GCIPL analysis (C=Central/S=Superior/I=Inferior/T=Temporal/N=Nasal). The vessel density of the macula and the optic disk were considered in parts of the central region and quadrants (M=Macula and D=Optic disc/S=Superior/I=Inferior/T=Temporal/N=Nasal). If a participant had no history of optic neuritis, the mean values of both eyes were analysed. If a participant had a history of optic neuritis, the non-affected eye was examined. Statistical analyses were done separately in pwMS without optic neuritis (ON-) and with optic neuritis (ON+). To interpret the correlation of cognitive status and OCT/OCTA measurements, Brief International Cognitive Assessment in Multiple Sclerosis (BICAMS, which includes SDMT, BVMT-R and CVLT-II) results in the period of OCT tests were analysed. In our study design, there was no healthy control. Because of the fact that education level might have caused differences in cognitive tests, we only included the pwMS with ≥12 years of education level. The participants who had MS relapse during cognitive assessments and OCT/OCTA or a history of bilateral optic neuritis were excluded from the study. Data on gender, age, diagnosis age, and EDSS were collected and analysed.

Statistical Analysis

Data were analysed using the IBM SPSS (Version 26.0. Armonk, NY: IBM Corp.) program. Normal distribution was determined by Kolmogorov-Smirnov/Shapiro-Wilk tests. According to the distribution results, appropriate statistical analysis methods were used. Chi-square tests were used to compare categorical variables between groups. If the distribution was normal, we used the Pearson correlation test for analysis. If the distribution was non-normal, a Spearman test was used. The correlation results were labelled the strength of the association for absolute values of correlation coefficients, 0.2-0.39 as weak, 0.4-0.59 as moderate, 0.6-0.79 as strong, and 0.8-1 as very strong. The statistical significance level was determined as $p<0.05$.

Results

A total of 84 pwMS were included in the study. Twenty-eight participants had a history of ON+ group, and 56 pwMS had no history of optic neuritis (ON- group). There were no differences between the groups regarding EDSS, BVMT-R, CVLT-II, SDMT, number of relapses, gender, diagnosing age and current age (p>0.05) (Table 1).

In the ON- group, 50 pwMS had OCT test results, and 56 had OCT-A results. So, 100 eyes in OCT and 112 in OCT-A were interpreted. The relapse number had a weak negative correlation with the inferior quadrant of OCTA-D (OCTA-D-I: ρ=-0.325, p=0.021). The thickness of GCIPL inferior and temporal quadrants exhibited a weak positive correlation with BVMT-R (Table 2). Only OCTA-D-I results had a weak negative correlation with SDMT in OCTA measurements (ρ=0.329, p=0.02, Table 2).

In the ON+ group, 27 pwMS had OCT results, and 28 had OCT-A results. The number of relapses had a negative correlation with RNFL-ST (ρ=-0.481, p=0.011). Only the SN quadrant of RNFL had a moderate negative correlation with the results of CVLT-II (ρ=-0.458, p=0.016). On the other hand, GCIPL, in all quadrants except the centrum, positively correlated with SDMT. Similar correlation results were detected between the inferotemporal/global thickness of RNLF and SDMT. Cognitive tests, relapse number, EDSS score or age did not show a correlation with OCT-A measurements (Table 3).

Discussion

The findings of this study indicated that certain parts of the retinal layer may suggest cognitive impairment in people with MS. However, vascular density in the retina may not be a reliable biomarker for the cognitive condition of people with relapsing-remitting MS.

The first study, published in 2008, revealed that retinal layer thickness can indicate cognitive status in pwMS. Temporal RNFL thickness was especially related to SDMT in this study (21). Studies demonstrated that average RNFL and GCIPL thickness might correlate with cognitive abilities in pwMS (19,22-25). The regions of RNFL and GCIPL might contribute to this relationship in different portions. For instance, the temporal region of RNFL especially demonstrates a positive correlation with SDMT in the studies (21,26). However, certain parts of the studies did not demonstrate the relation between cognition and the thickness of the retinal layers (27,28). Petracca et al. (29) conducted a study in people with primary progressive MS, indicating that only GCIPL atrophy represents cognitive impairment. The history of optic neuritis causes severe atrophy and may mask the cognitive relations of it (22). Some studies analysed the OCT results of pwMS with and without optic neuritis (21). To avoid this situation, we divided our cohort into ON+ and ON- groups and included the only non-affected eye for analyses in the ON+ group. ON- group, inferior and temporal quadrants of GCIPL negatively correlated in specific cognitive tests. Atrophy of RNLF did not show a correlation with cognitive impairments (Table 2). These findings contradict the current literature. However, the negative correlation was quite weak. It could be due to the cognitive reserve of pwMS. People with MS who had similar disability levels and similar brain lesion load may have differences in cognitive tests. Cognitive reserve, which occurs through education, intelligence, etc. can explain this situation. Cognitive reserve can play a protective role in cognitive skills and moderate the results of cognitive tests in pwMS (30,31). Some participants might have a high cognitive reserve, which can cause these results in our study. On the other hand, studies found no correlation between retinal layer thickness and cognition in pwMS with low EDSS scores (27,28). Our participants also have low EDSS scores, and we found no association between cognitive skills and OCT measurements in the ON- group (The median EDSS score in ON- =0.5). Axonal loss and neurodegeneration in pwMS can be seen throughout the disease. However, they are more evident in progressive and high-disability patients (32). So, brain atrophy, cognitive impairments and axonal loss in pwMS are more evident in these groups.

Table 1. Demographic variables of pwMS with optic neuritis (ON+) and without optic neuritis (ON-)

	ON+	ON-	Statistics (p)
Total participants, n	28	56	
Gender, n of females, percentage	14/28 (50%)	40/56 (71.4%)	0.053
Age, median, Min.-Max.	29.5, 19-47	34, 18-56	0.414
Diagnosing age, median, Min.-Max.	26, 16-40	27, 16-44	0.872
Relapse number, median, Min.-Max.	2, 1-8	2, 1-10	0.957
EDSS score, median, Min.-Max.	0.5, 0-5.5	1, 0-2.5	0.205
BVMT-R, median, Min.-Max.	29.5, 11-36	29.5, 11-36	0.996
CVLT-II±SD	52.89±13.97	54.84±10.62	0.385
SDMT±SD	53.79±12.56	52.45±11.26	0.891

n: Number, EDSS: Expanded Disability Status Scale, BVMT-R: Brief Visuospatial Memory Test-Revised, CVLT-II: California Verbal Learning Test-II, SDMT: Symbol Digit Modalities Test, SD: Standard deviation, Min.-Max.: Minimum-maximum

Table 2. Correlation analysis of ON- pwMS

	BVMT-R	SDMT	CVLT-II	EDSS	N of relapses	Current age	MS diagnosing age
RNFL-G	ρ=-0.183	r=0.149	r=0.029	ρ=0.010	ρ=-0.124	ρ=-0.088	ρ=0.050
RNFL-ST	ρ=-0.185	r=0.260	r=0.074	ρ=-0.050	ρ=-0.145	ρ=0.045	ρ=0.212
RNFL-SN	ρ=-0.227	r=0.157	r=-0.188	ρ=0.008	ρ=-0.135	ρ=-0.148	ρ=-0.087
RNFL-IT	ρ=-0.168	r=0.040	r=-0.027	ρ=-0.031	ρ=0.030	ρ=0.026	ρ=0.125
RNFL-IN	ρ=-0.275	r=-0.181	r=0.021	ρ=0.180	ρ=0.023	ρ=-0.022	ρ=0.025
RNFL-N	ρ=-0.067	r=0.167	r=0.234	ρ=-0.022	ρ=-0.086	ρ=-0.050	ρ=0.075
RNFL-T	ρ=-0.096	r=0.117	r=-0.047	ρ=0.102	ρ=-0.216	ρ=0.030	ρ=0.235
GCIPL-C	ρ=0.13	ρ=0.275	ρ=-0.117	ρ=0.000	ρ=-0.08	ρ=-0.104	ρ=0.02
GCIPL-S	ρ=-0.256	ρ=0.156	ρ=-0.106	ρ=0.089	ρ=-0.218	ρ=-0.076	ρ=0.114
GCIPL-I	ρ=-0.34 p=0.014	ρ=0.117	ρ=-0.059	ρ=0.163	ρ=-0.167	ρ=-0.032	ρ=0.31
GCIPL-N	ρ=-0.24	ρ=0.278	ρ=-0.198	ρ=0.107	ρ=-0.251	ρ=-0.211	ρ=-0.028
GCIPL-T	ρ=-0.303 p=0.032	ρ=0.179	ρ=-0.138	ρ=-0.000	ρ=-0.080	ρ=-0.104	ρ=0.020
OCTA-M-C	ρ=-0.01	r=-0.168	r=-0.254	ρ=-0.055	ρ=0 .011	ρ=-0.003	ρ=-0.052
OCTA-M-S	ρ=-00.141	r=-0.088	r=-0.045	ρ=0.242	ρ=-0.004	ρ=0.136	ρ=0.057
OCTA-M-I	ρ=0.089	ρ=0.022	ρ=0.08	ρ=0.005	ρ=-0.06	ρ=0.131	ρ=0.096
OCTA-M-N	ρ=0.222	ρ=-0.11	ρ=0.035	ρ=-0.02	ρ=-0.048	ρ=0.086	ρ=0.121
OCTA-M-T	ρ=-0.005	r=-0.014	r=0.064	ρ=-0.111	ρ=-0.154	ρ=-0.074	ρ=-0.154
OCTA-D-C	ρ=-0.048	r=0.044	r=0.109	ρ=-0.114	ρ=-0.114	ρ=-0.032	ρ=-0.037
OCTA-D-S	ρ=0.092	r=0 .017	r=-0.257	ρ=-0.203	ρ=-0.203	ρ=-0.355	ρ=-0.273
OCTA-D-I	ρ=0.178	ρ=0.195	**ρ=0.329 p=0.02**	ρ=-0.109	**ρ=-0.325 p=0.021**	ρ=-0.172	ρ=0.007
OCTA-D-N	ρ=-0.137	r=-0.123	r=0.144	ρ=-0.036	ρ=-0.036	ρ=0.073	ρ=0.162
OCTA-D-T	ρ=-0.162	r=-0.123	r=-0.239	ρ=0.2	ρ=-0.191	ρ=-0.11	ρ=0.081
BVMT-R	-	**ρ=0.296 p=0.027**	**ρ=0.408 p=0.002**	ρ=-0.201	ρ=-0.018	ρ=-0.157	ρ=-0.18
SDMT	**ρ=0.296 p=0.027**	-	**r=0.4 p=0.002**	ρ=-0.205	ρ=0.144	**ρ=-0.450 p=0.001**	**ρ=-0.341 p=0.01**
CVLT-II	**ρ=0.408 p=0.002**	**r=0.4 p=0.002**	-	ρ=-0.183	ρ=0.02	ρ=0.000	ρ=0.079
EDSS	ρ=-0.201	ρ=-0.205	ρ=-0.183	-	ρ=0 .075	**ρ=0.271 p=0.043**	ρ=0.078
N of relapses	ρ=-0.018	ρ=0.144	ρ=0.02	ρ=0.075	-	ρ=0.226	ρ=-0.183
Current age	ρ=-0.157	**ρ=-0.450 p=0.001**	ρ=0.000	**ρ=0.271 p=0.043**	ρ=0.226	-	**ρ=0.78 p=0.000**
MS diagnosing age	ρ=-0.18	**ρ=-0.341 p=0 0.01**	ρ=0.079	ρ=0.078	ρ=-0.183	**ρ=0.78 p=0.000**	-

A total of 50 OCT results and 56 OCTA results were considered. RNFL: Retinal Nerve Fiber Layer, G: Global, SN: Superiornasal, ST: Superiortemporal, IT: Inferotemporal, IN: Inferonasal, N: Nasal, T: Temporal, GCIPL: Ganglion Cell Internal Plexiform Layer, C: Central, S: Superior, I: Inferior, OCTA: Optical Coherence Tomography-Angiography, M: Macular, D: Disc, BVMT-R: Brief Visuospatial Memory Test-Revised, SDMT: Symbol Digit Modalities Test, CVLT-II: California Verbal Learning Test-II, EDSS: Expanded Disability Status Scale, N: Number, MS: Multiple sclerosis

Table 3. Correlation analysis of ON+ pwMS

	BVMT-R (ρ)	SDMT (ρ)	CVLT-II (ρ)	EDSS (ρ)	N of relapses (ρ)	Current age (ρ)	MS diagnosing age (ρ)
RNFL-G	-0.192	**ρ=0.424 p=0.028**	-0.043	-0.037	-0.272	-0.153	0.031
RNFL-ST	0.234	0.354	0.049	-0.183	**ρ=-0.481 p=0.011**	-0.118	0.080
RNFL-SN	-0.308	0.025	**ρ=-0.458 p=0.016**	-0.074	-0.283	0.092	0.108
RNFL-IT	0.094	**ρ=0.466 p=0.014**	0.270	-0.064	-0.332	-0.276	-0.086
RNFL-IN	-0.356	0.121	-0.243	-0.077	-0.161	0.101	0.114
RNFL-N	-0.155	0.261	-0.108	0.290	0.046	0.102	0.264
RNFL-T	0.191	0.260	0.134	-0.220	-0.124	-0.291	-0.167
GCIP-C	0.001	0.082	0.049	-0.038	0.217	0.315	0.363
GCIP-S	0.342	**ρ=0.542 p=0.003**	0.364	-0.149	-0.181	-0.358	-0.183
GCIP-I	0.108	**ρ=0.401 p=0.038**	0.154	-0.132	-0.167	-0.251	-0.107
GCIP-N	0.167	**ρ=0.441 p=0.021**	0.239	-0.081	-0.080	-0.213	-0.074
GCIP-T	0.225	**ρ=0.412, p=0.033**	0.365	-0.055	0.023	-0.278	-0.133
OCTA-M-C	0.022	0.056	0.001	0.046	-0.053	0.185	0.245
OCTA-M-S	0.150	0.280	0.088	-0.039	0.215	-0.310	-0.291
OCTA-M-I	0.172	0.003	-0.067	0.103	0.257	0.131	-0.029
OCTA-M-N	0.252	0.066	0.175	-0.217	0.188	-0.017	0.038
OCTA-M-T	0.103	0.120	-0.074	-0.034	-0.021	-0.002	0.071
OCTA-D-C	-0.061	0.182	-0.085	0.069	-0.104	-0.355	-0.336
OCTA-D-S	-0.278	-0.349	-0.246	0.080	-0.122	0.077	0.164
OCTA-D-I	-0.104	0.002	-0.014	0.075	-0.038	0.062	0.201
OCTA-D-N	-0.100	0.191	-0.189	-0.102	-0.207	0.036	0.187
OCTA-D-T	0.086	0.222	0.297	0.026	-0.062	-0.050	-0.098
BVMT-R	-	**ρ=0.432 p=0.022**	**ρ=0.724 p=0.000**	**ρ=-0.447 p=0.017**	0.001	-0.173	-0.144
SDMT	**ρ=0.432 p=0.022**	-	**ρ=0.401 p=0.034**	-0.28	**ρ=-0.398 p=0.036**	-0.190	-0.016
CVLT-II	**ρ=0.724 p=0.000**	**ρ=0.401 p=0.034**	-	-0.195	0.001	-0.161	-0.141
EDSS	**ρ=-0.447 p=0.017**	-0.28	-0.195	-	0.122	0.366	0.307
N of relapses	0.001	**ρ=-0.398 p=0.036**	0.001	0.122	-	0.281	0.118
Current age	-0.173	-0.190	-0.161	0.366	0.281	-	**ρ=0.861 p=0.000**
MS diagnosing age	-0.144	-0.016	-0.141	0.307	0.118	**ρ=0.861 p=0.000**	-

A total of 27 OCT and 28 OCTA results were considered. RNFL: Retinal Nerve Fiber Layer, G: Global, SN: Superiornasal, ST: Superiortemporal, IT: Inferotemporal, IN: Inferonasal, N: Nasal, T: Temporal, GCIPL: Ganglion Cell Internal Plexiform Layer, C: Central, S: Superior, I: Inferior, OCTA: Optical Coherence Tomography-Angiography, M: Macular, D: Disc, BVMT-R: Brief Visuospatial Memory Test-Revised. SDMT: Symbol Digit Modalities Test, CVLT-II: California Verbal Learning Test-II, EDSS: Expanded Disability Status Scale, N: Number, MS: Multiple sclerosis

The low correlation between retinal layer thickness and cognition in pwMS with low disability levels might be the main cause of these results. The disability levels of ON+ participants are similar to ON- participants (Median EDSS score in ON- =0.5 vs ON+ =1). However, in ON+, GCIPL had a moderate positive correlation with SDMT. A similar correlation was detected with the RNFL-IT quadrant and global RNLF. The SDMT evaluates information processing speed, which is the key cognitive function impaired in pwMS. It is also impaired during the early stages of MS. Thus, this relationship may be considered in this context (Table 3). The atrophy of the retinal layers might be a consequence of asymptomatic optic nerve lesions. Asymptomatic optic nerve lesions might be the primary link between brain volume loss, cognitive testing, and retinal atrophy (33). The analysis of asymptomatic optic nerve lesions may provide more information about the fact that there is no relationship between cognition and retinal atrophy in the low EDSS group. The different correlation results in the ON- and ON+ groups might be related to different percentages of asymptomatic optic nerve lesions in both groups. The participants in ON+ might have experienced more asymptomatic optic nerve lesions than the ON- group.

Microvascular damage and related hypoxia can contribute to neurodegeneration and disability in pwMS. Hypoxia in cortical and white matter regions was high in pwMS, especially with a high EDSS score and secondary progressive subtype (4,34,35). In secondary progressive MS, cortical hypoperfusion might related to low cognitive status (36). However, in another study, cortical hypoxia was not correlated with cognitive measurements in relapsing-remitting pwMS (37). Abnormal retinal microcirculation in pwMS with and without optic neuritis was demonstrated in different studies (7,11-13). However, the relationship between retinal microvascular density and disability levels in pwMS is not clear. Different studies indicated different results. A study from Turkey demonstrated no relationship between disability levels and retinal microvascular density (12). Lower superficial vessel density might be related to higher disability levels (11). However, Mrabet et al. (13) did not find this correlation in their study. They indicated that choriocapillaris density shows an inverse correlation with EDSS scores. A positive correlation between disability status and superficial retinal density was detected in another study (10). Further, retinal microvascular density can improve with time in pwMS with stable disease (38). Different demographic and clinical variables might cause these differences. Our study found no relation between OCT-A measurements and EDSS and age in both groups. Only the number of relapses exhibited a weak positive correlation with OCTA-D-I in the ON- group. Retinal superficial and deep vascular rarefication were found to be associated with grey matter atrophy independent of ganglion cell layer thickness in pwMS with low disability levels. Even a decrease in these densities was related to decreased grey matter volume and increased disability levels. Longitudinal loss in deep and superficial retinal vessels was detected more frequently in pwMS, which had worsening SDMT scores (14). This study investigated the SDMT and OCT-A measurements only in longitudinal courses. Our study considered the association between vessel density and cognition cross-sectional. Also, we considered the total BICAMS results of our participants. We found a positive correlation between CVLT-II and inferior optic disc vessel density in the ON- group. The other parts of OCT-A do not correlate with other cognitive tests (Tables 2 and 3).

Study Limitations

Our study has several limitations. The retrospective nature of the study focusing on OCT and OCT-A examinations inherently limited the participant pool, as these tests were performed based on clinical indications rather than as part of a standardized protocol. The OCT and OCT-A are ordered by ophthalmologists and neurologists in the appropriate situations. Because we had no healthy controls, we only included the pwMS who have ≥12 years of education. Larger studies and studies that include healthy controls can provide more information about the relationship between OCT, OCT-A, and cognition in wider pwMS populations. As previously stated, cognitive reserve, pwMS with a low disability, and relapsing form may create distinctions in our study. Different results between groups related to cognitive and retinal measurements might stem from a low number of participants, especially in the ON+ group, or different clinical characteristics between the groups, such as different brain atrophy stages, lesion numbers etc. Further studies considering these variables might explain these differences. Even though there are a lot of studies regarding retinal later thickness and cognitive skills, we found limited studies about retinal microcirculation and cognition. Although our results indicated a limited correlation between retinal vessel density in the inferior optic disc quadrant and cognition, further studies can be designed in wider populations and pwMS with higher disability levels.

Conclusion

The study found that OCT is limited in reflecting cognitive impairments in ON- pwMS with low disability levels. However, certain regions of GCIPL and RNFL may demonstrate a positive correlation with SDMT in ON+ pwMS. The retinal microcirculation and cognitive correlation were weak, but further studies can provide more information.

Ethics

Ethics Committee Approval: This cross-sectional study was approved by the Non-invasive Research Ethics Board of Dokuz Eylul University (protocol no.: 6546-GOA, decision no.: 2021/22-03).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: E.K., D.O., F.G., A.Y., C.B., Concept: S.O., A.Y., C.B., Design: S.O., O.S., Data Collection or Processing: S.O., D.O., F.G., O.S., A.Y., Analysis or Interpretation: S.O., E.K., O.S., Literature Search: S.O, E.K., Writing: S.O, E.K., A.Y., C.B.

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RESEARCH ARTICLE

Exploring the Relationship Between Sleep Quality and Fatigue, Quality of Life, Daytime Sleepiness, and Anxiety-depression Levels in Patients with Multiple Sclerosis

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Abstract

Objective: Multiple sclerosis (MS) is a chronic neurological disorder often linked with fatigue and poor sleep quality, both of which significantly affect quality of life and mental health. This study aimed to explore the relationship between sleep quality and fatigue, quality of life, daytime sleepiness, and anxiety-depression in patients with MS (pwMS).

Materials and Methods: A cross-sectional study was conducted with 52 pwMS (16 with poor sleep quality, 36 without), recruited from a neurology clinic. Sleep quality was assessed using the Pittsburgh sleep quality index (PSQI), fatigue with the modified fatigue impact scale (MFIS), daytime sleepiness with the Epworth sleepiness scale (ESS), anxiety and depression using the hospital anxiety and depression scale (HADS), and quality of life with the preference-based multiple sclerosis index (PBMSI). Participants were categorized into two groups based on PSQI scores: Those with poor sleep quality and those without. The groups were compared based on patient-reported outcomes, and correlations between these variables and clinical characteristics (e.g., expanded disability status scale scores, disease duration) were examined.

Results: Participants with poor sleep quality reported higher MFIS scores across the physical, cognitive, and psychosocial domains compared to those without poor sleep quality, though these differences were not statistically significant. Anxiety was significantly higher in the poor sleep quality group ($p=0.043$), and there was a positive correlation between poor sleep quality and increased anxiety ($r=0.336$, $p<0.05$). No significant differences were found in ESS or PBMSI scores between the groups. Additionally, a significant correlation was observed between the number of relapses, and the MFIS-physical, MFIS-cognitive, MFIS-total scores, and the PSQI score.

Conclusion: This study underscores the relationship between sleep quality, fatigue, anxiety, and the number of relapses in pwMS. Improving sleep quality may help reduce fatigue and anxiety, thereby improving overall well-being. The results suggest that these factors should be evaluated and addressed together in managing MS.

Keywords: Fatigue, multiple sclerosis, sleep quality

Introduction

Multiple sclerosis (MS) is a chronic, progressive demyelinating disease that affects more than 2.5 million people globally, typically in young adults aged 20-40, with a higher prevalence in women (1). While the precise incidence in Turkey is unclear, it is estimated to be around 40 per 100,000 individuals. Recent epidemiological studies suggest a rising trend in both prevalence and incidence rates (2).

Sleep disturbances, which encompass a variety of sleep issues, symptoms, and diagnoses, affect more than 50% of patients with MS (pwMS), who report sleep disruptions or poor sleep quality (3). pwMS are more likely to experience conditions such as insomnia, sleep apnea, restless leg syndrome, and narcolepsy compared to the general population (4).

Fatigue and sleep disturbances are frequently reported as co-occurring symptoms in pwMS and can significantly impact

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quality of life (5,6). Fatigue affects up to 90% of pwMS and is characterized by persistent exhaustion, weakness, or tiredness. It is a major cause of unemployment, early retirement, and disability in this group (7). MS-related fatigue is especially difficult to assess and manage due to its multidimensional nature (e.g., physiological, cognitive, and behavioral aspects), its subjective experience, and its overlap with other symptoms and comorbidities, such as sleep disturbances (8).

Depression is commonly associated with MS, with a prevalence rate of up to 50% (9). Depression can present as fatigue, and its symptoms (such as loss of motivation and anhedonia) are often mistaken for MS-related fatigue, making the differential diagnosis more challenging. Research has shown a longitudinal relationship between depression and fatigue (10). Even when depression does not directly contribute to fatigue, addressing and treating it is crucial due to its significant effect on quality of life (11). Additionally, over 60% of pwMS report chronic sleep disturbances, which contribute to daytime sleepiness, worsening both fatigue and depression (12). Studies have also indicated that anxiety levels may be related to sleep quality in pwMS (13).

Considering the negative impact of symptoms like fatigue, anxiety-depression, and daytime sleepiness on functionality, it is important to understand the role of sleep quality as a potential contributing factor. Thus, this study aimed to explore the relationship between sleep quality and factors such as fatigue, quality of life, daytime sleepiness, and anxiety-depression levels in pwMS while identifying contributing factors. Moreover, examining the differences and relationships between sleep quality and clinical characteristics, such as disability level, disease duration, and number of relapses, could provide insights into the sleep disturbances experienced by pwMS.

Materials and Methods

Study Design

This cross-sectional study involved pwMS who voluntarily participated during routine check-ups at MS Clinic of the Neurology Department at Van Yuzuncu Yil University Medical Faculty Hospital. Ethical approval was granted by the Non-Invasive Research Ethics Committee of Van Yuzuncu Yil University Faculty of Health Sciences on October 18, 2024, under approval number 2024/11-26.

Participants

The study by Al-dughmi and Siengsukon (14) examined the relationship between sleep quality and fatigue. The study found a correlation of r^2=0.388 (p=0.005) between the total Pittsburgh sleep quality index (PSQI) score, used to assess sleep quality, and fatigue levels. The effect size of this relationship was calculated to be 0.62. Using G*Power (version 3.1) software, the minimum required sample size was determined to be at least 20 patients, with an effect size of 0.62, a power of 95%, and an error probability of 0.05.

Inclusion criteria were a confirmed MS diagnosis, age between 18 and 65 years, no relapses in the past 3 months, and willingness to participate. Exclusion criteria included severe musculoskeletal, cardiovascular, pulmonary, or metabolic conditions that could prevent participation, other neurological disorders, severe cognitive impairments that might interfere with completing the tests, or the use of sleep-related or sleep-inducing medications.

Outcomes

Demographic Data

Data was gathered on age, gender, weight, height, body mass index, education level, occupation, employment status, marital status, and clinical factors (e.g., MS type, Expanded Disability Status Scale (EDSS) score, time since diagnosis, relapse history, and medications).

EDSS

The EDSS is a widely recognized scale used to evaluate neurological disability in pwMS through clinical evaluations and mobility tests. Scores range from 0 (normal) to 10.0 (death due to MS). Scores from 1.0 to 4.5 reflect full ambulation, while scores between 5.0 and 9.5 indicate various degrees of mobility impairment. Scores above 7.0 suggest the patient is wheelchair or bed-bound. The EDSS assesses functions such as pyramidal, cerebellar, sensory, visual, brainstem, bladder, bowel, and cerebral (15).

PSQI

The PSQI, developed by Buysse et al. (16) and adapted into Turkish by Ağargün et al. (17), is a self-report tool used to evaluate sleep quality over the past month. It includes 19 items across 7 components, each scored from 0 to 3, with a total range of 0-21. A score above 5 indicates poor sleep quality (16,17).

Epworth Sleepiness Scale (ESS)

The ESS evaluates daytime sleepiness with eight questions rated from 0 to 3, evaluating the likelihood of dozing off in various daily situations. A score of 10 or higher indicates excessive daytime sleepiness (18). The Turkish version has been validated (19).

Modified Fatigue Impact Scale (MFIS)

The MFIS, commonly used in clinical research, measures the impact of fatigue on physical, cognitive, and social functioning through 21 questions rated from 0 to 4. Lower scores indicate less fatigue (20). The Turkish version has been validated for use with Turkish pwMS (21).

Hospital Anxiety and Depression Scale (HADS)

The HADS evaluates anxiety and depression in pwMS using 14 items (7 for anxiety and 7 for depression), scored on a 0-3

Likert scale. Higher scores indicate greater severity (22). The Turkish version was validated by Aydemir (23), confirming its appropriateness for pwMS.

Preference-based Multiple Sclerosis Index (PBMSI)

The PBMSI is a patient-reported measure that covers five areas: Walking, fatigue, mood, concentration, and roles. Each item has three response options, scoring between 0 (worst) and 1 (best) (24). The Turkish version was validated by Kahraman et al. (25).

Statistical Analysis

Data analysis was performed using IBM SPSS Statistics (Version 25.0, Armonk, NY, IBM Corp.). The normality of the data distribution was assessed using the Kolmogorov-Smirnov test and histograms. Since continuous variables showed normal distribution, the mean and standard deviation were reported with a 95% confidence interval. For categorical variables, frequency and percentage values were provided. Comparisons of clinical and demographic factors and patient-reported outcomes between the groups (with and without poor sleep quality) were made using an independent samples t-test for continuous data and the chi-squared test for categorical data. The relationship between sleep quality and other variables was evaluated using Pearson correlation coefficients. Correlation values were interpreted as small (≤0.30), moderate (0.31-0.59), or strong (≥0.60). Statistical significance was set at $p<0.05$ (26).

Results

Table 1 displays the demographic and clinical characteristics of pwMS, categorized into two groups based on the presence or absence of poor sleep quality. The group with poor sleep quality (n=16) had a mean age of 32.50±10.12 years, while the group without poor sleep quality (n=36) had a slightly lower mean age of 29.69±8.36 years (p=0.301). In terms of gender, females made up a larger proportion in both groups, with 87.5% in the poor sleep quality group and 63.9% in the group without poor sleep quality. The mean EDSS score was higher in the poor sleep quality group (1.59±1.54) compared to the group without poor sleep quality (1.08±1.23). Disease duration was also slightly longer in the poor sleep quality group (7.13±5.27 years) than in the other group (5.89±4.32 years). Similarly, the number of relapses was higher in the poor sleep quality group (3.94±2.49) compared to the group without poor sleep quality (2.64±1.64). Although some differences in demographic and clinical characteristics were observed between the groups, none of these differences reached statistical significance, indicating similar baseline characteristics in terms of age, gender, EDSS scores, disease duration, and MS type.

Table 2 presents a comparison of patient-reported outcomes between pwMS with poor sleep quality (n=16) and those without (n=36). There was no significant difference in PBMSI scores between the groups, with the mean score being 0.64±0.24 for the poor sleep quality group and 0.70±0.18 for the group without poor sleep quality (F=0.836, p=0.243). In the MFIS domains, participants with poor sleep quality reported higher scores in the physical (15.13±11.36 vs. 10.56±8.50, p=0.114), cognitive (17.69±12.85 vs. 12.75±9.23, p=0.122), and psychosocial (3.19 3.06 vs. 2.06±2.29, p=0.145) subscales compared to those without poor sleep quality. Although these differences suggest higher fatigue in the poor sleep quality group, none were statistically significant. The MFIS-total score also suggested higher overall fatigue in the poor sleep quality group (36.0±26.85) compared to the group without poor sleep quality (25.33±18.06), but this difference was not statistically significant (F=6.789, p=0.098). The ESS score was slightly lower in the poor sleep quality group (3.88±3.84) compared to the non-poor sleep quality group (4.61±4.79), with no significant difference (p=0.591). Regarding psychological outcomes, the HADS results showed that depression scores (HADS-D) were

Table 1. Demographic and clinical characteristics of the participants

	pwMS with poor sleep quality (n=16)	pwMS without poor sleep quality (n=36)	p-value
Age (years)	32.50±10.12	29.69±8.36	0.301
Gender, n (%)			
Female	14 (87.5%)	23 (63.9%)	0.083
Male	2 (12.5%)	13 (36.1%)	
EDSS score (Min.-Max.)	1.59±1.54 (0-5.5)	1.08±1.23 (0-5.0)	0.208
Disease duration of MS (years)	7.13±5.27	5.89±4.32	0.377
Number of relapses	3.94±2.49	2.64±1.64	0.070
MS type, n (%)			
RRMS	15 (93.8%)	35 (97.2%)	0.548
PPMS	1 (6.2%)	1 (2.8%)	

EDSS: Expanded disability status scale, MS: Multiple sclerosis, RRMS: Relapsing-remitting MS, PPMS: Primary progressive MS, pwMS: Patients with multiple sclerosis, Min.-Max.: Minimum-maximum

higher in the poor sleep quality group (8.0±4.87) than in the non-poor sleep quality group (6.22±4.15), but the difference was not significant (p=0.183). However, anxiety scores (HADS-A) were significantly higher in the poor sleep quality group (9.13±5.24) compared to the non-poor sleep quality group (6.25±4.29), with a statistically significant difference (p=0.043).

While several measures, particularly related to fatigue and depression, indicated higher symptom burdens in pwMS with poor sleep quality, only the HADS-A showed a statistically significant difference between the groups.

Table 3 shows the correlation coefficients between sleep quality, patient-reported outcomes, and clinical characteristics in pwMS. Notably, HADS-A was positively correlated with the PSQI (r=0.336, p<0.05), indicating that poorer sleep quality is linked to higher anxiety. Additionally, the number of relapses showed a moderate correlation with the PSQI score (r=343, p<0.05). A small correlation was found between the MFIS-physical, MFIS-cognitive, and MFIS-total scores with the PSQI score (p<0.05).

Discussion

This study examined the relationship between sleep quality, fatigue, quality of life, daytime sleepiness, and anxiety-depression levels in pwMS. The results indicated a connection between sleep quality and fatigue (physical, cognitive, and total MFIS scores), the number of relapses, and anxiety levels in pwMS. A significant difference was observed between the groups in terms of anxiety levels.

Although both groups (with and without poor sleep quality) shared similar demographic and clinical characteristics, those with poor sleep quality reported higher levels of fatigue in the physical, cognitive, and psychosocial domains. While the differences in MFIS scores were not statistically significant, the trend suggests that poor sleep quality may worsen fatigue in pwMS. This finding is consistent with previous studies that show poor sleep quality can exacerbate fatigue, likely due to disrupted restorative sleep processes (27,28).

A key finding of this study was the higher anxiety levels in pwMS with poor sleep quality, as measured by the HADS-A. The correlation between poor sleep quality and increased anxiety (r=0.336, p<0.05) highlights the bidirectional relationship between sleep and mental health. Anxiety may contribute to poor sleep quality by increasing arousal, while poor sleep may worsen anxiety symptoms (29). AlSaeed et al. (30) explored factors that could reduce anxiety levels and identified MS relapse, physical inactivity, and fatigue as influential factors in anxiety. In our study, we found that anxiety, fatigue, and the number of relapses were related to sleep quality. Based on these results, we hypothesize that these factors interact in a cyclical manner. While depression scores were higher in the poor sleep quality group, the difference was not statistically significant, suggesting that the relationship between depression and poor sleep quality in MS may be more complex or influenced by other factors.

Interestingly, no significant differences in daytime sleepiness (ESS scores) or quality of life (PBMSI scores) were found between the groups. This suggests that the effects of poor sleep quality may be more evident in terms of fatigue and psychological distress rather than noticeable daytime sleepiness. However, the positive correlation between ESS scores and MFIS subscales, despite not reaching statistical significance, indicates that individuals with higher daytime sleepiness tend to report more fatigue.

These findings emphasize the need for comprehensive management strategies in MS care. Addressing poor sleep quality could help reduce fatigue and anxiety, potentially improving overall quality of life. Clinicians should consider regularly screening for sleep issues and conducting mental health assessments as part of MS management, especially for patients with high fatigue or anxiety levels. Interventions aimed at improving sleep quality, such as cognitive-behavioral therapy for insomnia or relaxation techniques, may provide beneficial outcomes.

Table 2. Comparison of patient-reported outcomes between the groups

	pwMS with poor sleep quality (n=16)	pwMS without poor sleep quality (n=36)	F	p-value
ESS	3.88±3.84	4.61±4.79	0.761	0.591
MFIS-physical	15.13±11.36	10.56±8.50	3.192	0.114
MFIS-cognitive	17.69±12.85	12.75±9.23	4.896	0.122
MFIS-psychosocial	3.19±3.06	2.06±2.29	2.965	0.145
MFIS-total score	36.0±26.85	25.33±18.06	6.789	0.098
HADS-D	8.0±4.87	6.22±4.15	0.445	0.183
HADS-A	9.13±5.24	6.25±4.29	0.339	0.043
PBMSI	0.64±0.24	0.70±0.18	0.836	0.243

ESS: Epworth sleepiness scale, pwMS: patients with multiple sclerosis, MFIS: Modified fatigue impact scale, HADS: Hospital anxiety and depression scale, PBMSI: Preference-based multiple sclerosis index

Table 3. Correlation coefficients between sleep quality, patient-reported outcome measures, and participant characteristics

Variables	Age	Disease duration	EDSS	Number of relapses	MFIS-physical	MFIS-cognitive	MFIS-psychosocial	MFIS-total score	PBMSI	ESS	HADS-A	HADS-D	PSQI-total
Age	1												
Disease duration	0.371**	1											
EDSS	0.376**	0.322*	1										
Number of relapses	-0.042	0.382**	0.251	1									
MFIS-physical	0.081	0.173	0.487**	0.243	1								
MFIS-cognitive	0.032	0.189	0.346*	0.286*	0.836**	1							
MFIS-psychosocial	0.178	0.180	0.445**	0.160	0.805**	0.714**	1						
MFIS-total score	0.074	0.192	0.443**	0.270	0.958**	0.953**	0.834**	1					
PBMSI	0.179	0.064	-0.087	-0.208	-0.547**	-0.556**	-0.527**	-0.583**	1				
ESS	-0.289*	-0.125	0.142	0.070	0.467*	0.420**	0.298*	0.452**	-0.207	1			
HADS-A	-0.078	-0.039	0.252	0.113	0.638**	0.554**	0.693**	0.643**	-0.614**	0.257	1		
HADS-D	0.021	0.145	0.309*	0.034	0.559**	0.516**	0.501**	0.565**	-0.304**	0.066	0.558**	1	
PSQI-total	0.023	0.116	0.133	0.343*	0.303*	0.297*	0.205	0.308*	-0.210	0.069	0.336*	0.243	1

EDSS: Expanded disability status scale, HADS: Hospital anxiety and depression scale, MFIS: Modified fatigue impact scale, PSQI: Pittsburgh sleep quality index, PBMSI: Preference-based multiple sclerosis index, ESS: Epworth sleepiness scale, *: Correlation is significant at the 0.05 level (2-tailed), **: Correlation is significant at the 0.01 level (2-tailed)

Study Limitations

The relatively small sample size may have limited the statistical power to detect significant differences in some measures. Future studies with larger cohorts could provide more insight into the relationships between these variables. Additionally, longitudinal studies are needed to examine the causal relationships and the effects of interventions targeting sleep quality on fatigue and mental health outcomes.

Conclusion

In conclusion, our study highlights the complex relationship between sleep quality, number of relapses, fatigue, and anxiety in pwMS. Our results identified factors that could influence sleep quality and emphasize the importance of evaluating and addressing them together.

Ethics

Ethics Committee Approval: Ethical approval was granted by the Non-Invasive Research Ethics Committee of Van Yuzuncu Yil University Faculty of Health Sciences on October 18, 2024, under approval number 2024/11-26.

Informed Consent: Informed consent was obtained.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.T.O., E.A., P.Y., V.C., Concept: A.T.O., E.A., P.Y., V.C., Design: A.T.O., E.A., P.Y., V.C., Data Collection or Processing: A.T.O., E.A., P.Y., V.C., Analysis or Interpretation: A.T.O., E.A., P.Y., V.C., Literature Search: A.T.O., E.A., P.Y., V.C., Writing: A.T.O., E.A., P.Y., V.C.

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RESEARCH ARTICLE

What is the Relationship Between Disability Level, Hip Adductor Spasticity, and Incontinence in People with Multiple Sclerosis? - A Pilot Study

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Abstract

Objective: This study aimed to examine the relationship between disability level, hip adductor spasticity, incontinence, pelvic floor dysfunction, and quality of life in patients with multiple sclerosis (pwMS).

Materials and Methods: Nineteen participants (11 females, 8 males) were included. Disability levels were assessed using the Expanded Disability Status Scale (EDSS). Spasticity was evaluated with the modified ashworth scale (MAS). Incontinence and pelvic floor dysfunction were assessed using the pelvic floor distress inventory-20 and its subscales [colorectal-anal distress inventory-8 (CRADI-8), urogenital distress inventory-6 (UDI-6)]. The impact on quality of life was measured with the international consultation on incontinence questionnaire-short form (ICIQ-SF), while overall health status was assessed using the king's health questionnaire (KHQ).

Results: The mean EDSS score was 2.23±1.67. No significant differences were observed between male and female participants for MAS-right, MAS-left, CRADI-8, UDI-6, ICIQ-SF, or the total KHQ score ($p>0.05$). A significant positive correlation was identified between disability levels and hip adductor spasticity, incontinence, pelvic floor dysfunction, and quality of life ($p<0.05$).

Conclusion: Routine evaluation of hip adductor spasticity, incontinence, pelvic floor dysfunction, and quality of life is recommended for pwMS, regardless of disability level or gender.

Keywords: Multiple sclerosis, hip adductor spasticity, incontinence, pelvic floor dysfunction, quality of life

Introduction

Multiple sclerosis (MS) is a neurodegenerative and inflammatory disease characterised by demyelination and secondary axon degeneration in the central nervous system (CNS), which usually occurs in young adults and is thought to be autoimmune (1). In the 2022 study, it is estimated that approximately 2.8 million people worldwide have MS and this number will increase over time (2). MS plaques/lesions are focal areas of demyelination with axonal loss and inflammation, commonly affecting the white matter and spinal cord, and may also involve the cerebral cortex. There are specific areas of MS in the CNS and the diagnosis is based on localisation (3,4).

MS, a chronic inflammatory disease, can manifest with symptoms such as reduced muscle strength, muscle tone, balance, coordination, and vision, along with severe fatigue, pain, bladder dysfunction, cognitive impairment, sensory disturbances, and emotional changes. The type and severity of symptoms vary between individuals (5). Spasticity, a velocity-dependent increase in muscle tone, is a significant feature of MS (6). It can affect both upper and lower limbs, impacting functionality and limiting daily activities (6,7). Spasticity often involves the muscles of the hip and lower extremities, including the hip flexors, hip adductors, and knee extensors. In cases of hip adductor spasticity, gait is markedly impaired, and mobility is restricted (8).

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In approximately 80% of patients with MS (pwMS), the most common MS plaques are located in the cervical spinal cord, particularly affecting the lateral corticospinal (pyramidal) and reticulospinal tracts. This involvement often leads to urinary system dysfunction (9). Urinary dysfunction is prevalent in MS because these tracts are responsible for the innervation of the bladder detrusor muscle and the external urethral sphincter (10). It is categorized into three types: storage, voiding, and postmicturition symptoms. Nearly 60% of pwMS experience moderate to severe urinary problems related to the disease. These symptoms can result in considerable morbidity and significantly impact quality of life, comparable to the effects of physical or cognitive impairments (10, 11).

Studies in the literature have documented urinary symptoms in pwMS (12-14). While it is known that the occurrence of urinary symptoms varies based on the location of CNS lesions, their relationship with disability levels and, specifically, hip adductor spasticity has not been explored. This study aimed was to examine the relationship between disability levels, hip adductor spasticity, incontinence, pelvic floor dysfunction, and quality of life in pwMS. The primary hypothesis was to assess the association between disability levels and incontinence, pelvic floor dysfunction, and quality of life. The secondary hypothesis was to assess the relationship between hip adductor spasticity and incontinence, pelvic floor dysfunction, and quality of life in pwMS.

Materials and Methods

This study was conducted as a cross-sectional observational study. It was completed in accordance with the principles of the Declaration of Helsinki at Zonguldak Bulent Ecevit University, Department of Neurology. All protocols and methods were approved by Zonguldak Bulent Ecevit University Ethics Committee (protocol no: 2024/22) and written consent was obtained from all patients.

Participants

Individuals aged 18-65 years with a confirmed diagnosis of MS by an experienced neurologist were included. Exclusion criteria included the presence of additional orthopedic or sensory issues in the lower extremities, any interventional procedures (such as botulinum toxin administration) within the past 6 months, lumbar disc herniation, or a neurogenic bladder.

Assessments

Demographic and clinical data of the participants were recorded. Disability levels were evaluated using the expanded disability status scale (EDSS), while hip adductor spasticity was assessed with the modified ashworth scale (MAS). Pelvic floor dysfunction and incontinence were assessed using the pelvic floor distress inventory-20 (PFDI-20), and the impact of incontinence on quality of life was measured with the international consultation on incontinence questionnaire-short form (ICIQ-SF). General health status was evaluated using the king's health questionnaire (KHQ). All assessments were conducted once and lasted 20-30 minutes.

Expanded Disability Status Scale (EDSS)

EDSS was used to determine the patients' level of disability. EDSS is most commonly used to assess the level of disability in pwMS. In this scale pyramidal, cerebral, cerebellar, brainstem, visual and sensory subparameters are evaluated. The EDSS is an ordinal rating system ranging from 0 (normal neurological status) to 10 (death due to MS). The EDSS scores the level of disability of patients after a detailed neurological examination. The determination of EDSS 4-6 is largely dependent on the characteristics of walking ability (15).

Assessment of Hip Adductor Spasticity

The MAS is the most widely used method for evaluating spasticity and is commonly applied in clinical settings. The patient is assessed while lying supine and relaxed. The joint is moved passively, repeatedly, and rapidly, with resistance being staged based on the examination findings (16). MAS is often used to assess spasticity in the hip adductors, knee extensors, and ankle plantar flexors, with scores ranging from 0 to 4. In this study, passive movement of the hip was performed with the patient in a supine position, and the increase in adductor muscle tone was evaluated for each leg. Patients were classified based on their MAS scores: no spasticity (0), mild spasticity (1 or 1+), moderate spasticity (2 or 3), and severe spasticity (4) (17).

PFDI-20

The PFDI-20 consists of 3 subscales and 20 questions that assess pelvic floor dysfunction related to the lower urinary system, colorectal-anal region, and pelvic organ prolapse (18). The overall score for pelvic floor dysfunction is calculated by summing the subscale scores, with higher scores indicating greater severity. This scale is used to evaluate pelvic organ prolapse, urinary and colorectal-anal symptoms resulting from pelvic floor dysfunction, as well as the level of discomfort associated with these symptoms. The scale includes the pelvic organ prolapse distress inventory-6 (POPDI-6), Colorectal-Anal Distress Inventory-8 (CRADI-8), and urinary distress inventory-6 (UDI-6), with a total of 20 items. Each subscale score ranges from 0 to 100, and the total score ranges from 0 to 300, where higher scores reflect increased discomfort related to pelvic floor symptoms (18). The scale was adapted into Turkish in 2010 (19). In this study, POPDI-6 was not used because it was not relevant for the male participants, and scores were obtained using the CRADI-8 and UDI-6.

ICIQ-SF

International incontinence survey modules are designed as universally applicable scales. The ICIQ-SF assesses the quality of life related to incontinence (20). It consists of six questions: "Date

of birth", "Gender", "How often do you experience incontinence?", "How much do you experience incontinence?", "How much does incontinence affect your daily life?", and "In which situations do you experience incontinence?". The total score ranges from 0 to 21, with higher scores indicating a greater negative impact on quality of life. The Turkish version of the questionnaire, which underwent validity and reliability testing in Turkish, was used to evaluate quality of life in this study (21).

KHQ

The KHQ is a tool recommended by international guidelines for assessing quality of life (22). The questionnaire consists of 10 main sections that evaluate general health status, the impact of incontinence, limitations in roles (physical and social limitations), personal relationships, emotional health, sleep energy levels, and symptom severity. In addition, there is a section called the symptom severity scale, which assesses the symptoms related to bladder issues. This section includes a key question: "How much do you think problems with your bladder affect your life?" It evaluates the impact and severity of bladder problems under various subheadings, such as pollakiuria, nocturia, sudden urge incontinence, stress incontinence, nocturnal enuresis, incontinence during sexual intercourse, frequent urinary tract infections, and bladder pain. The symptom severity scale is scored from 0 (best) to 30 (worst), while the scores for all other subscales range from 0 (best health) to 100 (worst health). The total for the entire questionnaire ranges from 0 (best) to 930 (worst). The Turkish version of the questionnaire has been validated and tested for reliability (23).

Statistical Analysis

Statistical analysis was conducted using the SPSS 22.0 software. The normality of the numerical variables was assessed with the Shapiro-Wilk test. Descriptive statistics were reported as the mean ± standard deviation and median (min-max) for numerical variables and as frequency and percentage for categorical data. Differences between groups for categorical variables were tested using the Spearman chi-squared test. For comparisons between two groups for numerical variables, the independent t-test was used when parametric test assumptions were met, and the Mann-Whitney U test was used when they were not. For comparisons among multiple groups for numerical variables, one-way ANOVA was applied when parametric assumptions were met, and Kruskal-Wallis ANOVA was used when they were not. The linear relationship between two numerical variables was evaluated using Pearson correlation analysis when parametric assumptions were met and Spearman correlation analysis when they were not. A p-value of <0.05 was considered statistically significant for all analyses.

Results

A total of 19 patients (11 females, 8 males) with a mean age of 39.31±12.80 years were included in the study. The mean EDSS score for the patients was 2.23±1.67. Of the patients, 15 (79%) were diagnosed with relapsing-remitting MS (RRMS), 3 (16%) with primary progressive MS (PPMS), and 1 (5%) with secondary progressive MS (SPMS). The demographic and clinical characteristics of the participants are provided in Table 1.

The hip adductor spasticity scores based on the MAS are shown in Table 2. Patients were distributed among MAS values of 0, 1, and 1+, with no patients exhibiting MAS values of 2, 3, and 4.

The scores for CRADI-8, UDI-6, ICIQ-SF, and the total KHQ score are displayed in Table 3.

No significant differences were found between men and women in terms of MAS-right, MAS-left, CRADI-8, UDI-6, ICIQ-SF, and the total KHQ score (p=0.642, p=0.924, p=0.298, p=0.177, p=0.310, and p=0.109, respectively).

The correlation analysis results are presented in Table 4. Higher disability levels were associated with increased MAS-left, CRADI-8, UDI-6, ICIQ-SF, and total KHQ scores (p=0.017,

Table 1. Descriptive characteristics of patients

	Minimum - maximum (n=19)	Mean ± SD (n=19)
Age (years)	20-62	39.31±12.80
Height (cm)	150-187	165.31±11.05
Weight (kg)	50-107	72.05 ±16.27
EDSS score	1-6	2.23±1.67
Duration of MS (year)	1-20	6.05±5.54

Table 2. Modified ashworth scale scores

MAS	Right n (%)	Left n (%)
0	15 (78.9%)	11 (57.9%)
1	1 (5.3%)	7 (36.8%)
1+	3 (15.8%)	1 (5.3%)

Table 3. Scores of pelvic floor dysfunction, incontinence and quality of life

	Minimum - maximum (n=19)	Mean ± SD (n=19)
CRADE-8	0-28	11.63±10.25
UDI-6	0-37	15.15±11.52
ICIQ-SF	0-19	5.15±6.17
Total score of KHQ	0-878	205.68±235.72

Table 4. Analysis of demographic data and tests' and scales' scores

		MAS-R	MAS-L	CRADE-8	UDI-6	ICIQ_SF	KHQ-Total
EDSS	r	0.429	0.541	0.629	0.496	0.564	0.580
	p	0.067	**0.017***	**0.004***	**0.031***	**0.012***	**0.009***
		CRADE-8	UDI-6		ICIQ_SF	KHQ-Total	
MAS-R	r	0.448	0.421		0.555	0.336	
	p	0.054	0.073		**0.014***	0.159	
MAS-L	r	0.331	0.330		0.627	0.474	
	p	0.166	0.167		**0.004***	**0.040***	
		ICIQ_SF			KHQ-Total		
CRADE-8	r	0.739			0.684		
	p	**<0.000***			**0.001***		
UDI-6	r	0.829			0.725		
	p	**<0.000***			**<0.000***		

EDSS: Expanded disability status scale, MAS-R: Modified ashworth scale-right, MAS-L: Modified ashworth scale-left, CRADE-8: Colorectal-anal distress inventory-8, UDI-6: Urinary distress inventory-6, ICIQ-SF: International consultation on incontinence questionnaire short form, KHQ: King's health questionnaire, *p-value <0.05

p=0.004, p=0.031, p=0.012, and p=0.009, respectively). Higher MAS-right scores were correlated with higher ICIQ-SF scores (p=0.014). Additionally, higher MAS-left scores were associated with higher ICIQ-SF (p=0.004) and total KHQ scores (p=0.040). Furthermore, higher CRADI-8 scores were linked to higher UDI-6, ICIQ-SF, and total KHQ scores (p<0.001, p<0.001, and p=0.001, respectively).

The correlation analyses between KHQ and EDSS, CRADI-8, and UDI-6 are presented in Table 5. A positive correlation was observed between disability status and the incontinence impact and emotions subscale scores (r=0.754, p<0.001; r=0.478, p=0.038, respectively). CRADI-8 scores showed a positive correlation with the incontinence impact, physical limitations, emotions, severity levels, and symptom severity scale (r=0.731, p<0.001; r=0.596, p=0.007; r=0.608, p=0.006; r=0.612, p=0.005; and r=0.481, p=0.037, respectively). Additionally, UDI-6 scores were positively correlated with general health status, incontinence impact, physical limitations, emotions, severity levels, and symptom severity scale (r=0.512, p=0.025; r=0.691, p=0.001; r=0.572, p=0.011; r=0.589, p=0.008; r=0.635, p=0.003; and r=0.563, p=0.012, respectively).

Discussion

This study investigated the disability level, hip adductor spasticity, incontinence, pelvic floor dysfunction, and quality of life in pwMS. In this pilot study, a correlation was identified between the disability level, hip adductor spasticity, incontinence, and incontinence-related quality of life in 19 patients with various types of MS. These findings suggest that patients with different MS types, varying levels of spasticity, genders, and particularly those with low EDSS scores, should be evaluated for incontinence and pelvic floor dysfunction.

MS is a condition with various clinical forms, and it has been reported that disease progression differs depending on the type. The disease typically begins with clinically isolated syndrome and progresses to RRMS, with studies indicating that a considerable number of RRMS patients eventually transition to SPMS (24). The sample in our study predominantly included individuals with RRMS, PPMS, and SPMS, reflecting the general MS population. Disability level was assessed using the EDSS score and disease duration, revealing that our population comprised mostly patients with low disability levels. Therefore, this study offers a novel perspective in the literature by examining incontinence, pelvic floor dysfunction, and quality of life in patients with low disability levels in MS.

Bladder dysfunction or incontinence, which is common in pwMS and impacts their quality of life, has been reported to affect nearly all patients 10 years after diagnosis (25). Studies have indicated that incontinence and quality of life are more significantly affected in patients with moderate disability and/or longer disease duration (26-28). In addition, some studies have focused primarily on women. Tekin et al. (12) reported a high incontinence rate in women with MS, which negatively affected their quality of life. Zecca et al. (27) included both men and women in their study, but only 28% of the participants were male. In our study, we identified a correlation between the EDSS score and incontinence, pelvic floor dysfunction, and quality of life in a population of both genders with low disability. The absence of significant gender differences in these parameters is an important finding. As we anticipated, we conclude that studies on pelvic floor dysfunction in the MS population should include both genders.

One of our hypotheses was that hip adductor spasticity could be linked to pelvic floor dysfunction and quality of life. In our

Table 5. The correlations between KHQ subparameters and EDSS, CRADE-8, UDI-6				
		EDSS	CRADE-8	UDI-6
General health status	r	0.415	0.342	0.512
	p	0.077	0.152	0.025*
Incontinence impact	r	0.754	0.731	0.691
	p	**0.000***	**0.000***	**0.001***
Role limitation	r	0.431	0.450	0.442
	p	0.066	0.053	0.058
Physical limitatitons	r	0.444	0.596	0.572
	p	0.057	**0.007***	**0.011***
Social limitations	r	0.359	0.431	0.429
	p	0.132	0.065	0.067
Personal relationships	r	0.277	0.129	0.045
	p	0.251	0.599	0.856
Emotions	r	0.470	0.608	0.589
	p	**0.038***	**0.006***	**0.008***
Sleep energy levels	r	0.358	0.345	0.344
	p	0.133	0.148	0.149
Severity measures	r	0.436	0.612	0.635
	p	0.062	**0.005***	**0.003***
Symptom severity scale	r	0.316	0.481	0.563
	p	0.187	**0.037***	**0.012***
Total KHQ score	r	0.580	0.684	0.725
	p	**0.009***	**0.001***	**0.000***

EDSS: Expanded disability status scale, CRADE-8: Colorectal-anal distress inventory-8, UDI-6: Urinary distress inventory-6, KHQ: King's health questionnaire, *: p-value <0.05

population, patients had low disability and minimal spasticity, and only hip adductor spasticity was found to be associated with quality of life. Marques et al. (29) demonstrated that the hip adductor muscles and pelvic floor muscles work synergistically and that training both is crucial for incontinence rehabilitation in healthy women. Although we anticipated that adductor muscle spasticity might be associated with incontinence and pelvic floor dysfunction in pwMS, we believe that the limited sample size prevented as from establishing this relationship. Furthermore, as seen in other studies (8), hip adductor spasticity may have impacted quality of life by hindering activities of daily living in our study.

Another finding of our study is that incontinence and pelvic floor dysfunction are linked to quality of life. While various factors influence quality of life in MS (30), our results showed that incontinence and pelvic floor dysfunction impact general health, emotions, social participation, and even sleep and energy levels, consistent with the literature (31). Early assessment and management of incontinence and pelvic floor dysfunction can enhance patients' participation in daily activities and improve quality of life.

Study Limitations

This is a pilot study, and to generalize the findings to the MS population, the sample size should be expanded to include patients with different MS types, varying disability levels, and hip adductor spasticity.

Conclusion

This pilot study demonstrated a correlation between disability level, hip adductor spasticity, incontinence, pelvic floor dysfunction, and quality of life. In pwMS, routine clinical assessments should address incontinence, pelvic floor function, and quality of life, regardless of disability level or gender, with potential effects identified earlier.

Ethics

Ethics Committee Approval: This study was approved by the Zonguldak Bulent Ecevit University Ethics Committee (protocol no: 2024/2).

Informed Consent: Each participant provided written informed consent.

Footnotes

Authorship Contributions

Concept: A.T.U., G.B.O.S., Design: A.T.U., G.B.O.S., Data Collection or Processing: A.T.U., M.A., Analysis or Interpretation: G.B.O.S., M.A., Literature Search: A.T.U., G.B.O.S., Writing: A.T.U., G.B.O.S., M.A.

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RESEARCH ARTICLE

Qualitative Insights into the Diagnosis, Treatment, and Socioeconomic and Psychological Challenges of Patients with Multiple Sclerosis in a Turkish Public Hospital

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Abstract

Objective: Objective of the study is to qualitatively evaluate challenges multiple sclerosis (MS) patients faced during diagnosis, treatment, and social life.

Materials and Methods: Population of our qualitative study consisted MS patients with expanded disability status scale score ≤5 (19-50 years of age) who were admitted to a public university hospital neurology department. Semi-structured question guide were applied via in-depth face-to-face interviews. Interviews wereaudio-recorded after permission. Twelve participants agreed to participate voluntarily, the recordings were transcribed, thematic analysis was conducted.

Results: "Attitude of family members and social circle", "problems came across" and "worries and coping mechanisms" were the most significant themes. Participants had anxiety after diagnosis because of fear of death, probabilityof losing functions and having no clue about what MS willbring in the future. Their families started to act more sensitively and with understanding after the diagnosis. While this situation was welcomed by some of the participants, some perceived this situation negatively a triggering factor for their feeling of insufficiency. Participants were exposed to stigma. One participant narrated he faced stigmatization due to his gait. Their educational lifeadversely affected. Participants faced situations such as not being hired or termination of employment. Probability of attacks to ocur at work could become an obstacle. Some participants stated it would be difficult to carry their responsibilities due to MS and start a family, so they would have difficulties in establishing romantic relationships. Some emphasized the disease would not cause a problem, but their partners' approach to MS was important. They were worried that their families would experience sadness and anxiety, that they would not be able to support their spouses and children if their disease progressed, they were also worried about risk of transmitting MS to their children. They developed coping strategiessuch as avoidance, religion, self-soothing.

Conclusion: Participants' knowledge about MS is limited. Families have a supportive attitude towards patients and takes teps to make participants' lives easier. Studies developing scales such as quantitatively measuring stigma or perceived empathy in MS patients can be recommended.

Keywords: Multiple sclerosis, challenges, qualitative study, social life, stigma

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Introduction

Multiple sclerosis (MS) is a chronic, autoimmune, demyelinating disease that frequently affects the central nervous system in young adults (1-5). The clinical signs and symptoms of MS include motor, sensory, autonomic, and cognitive impairments that vary according to the region of the central nervous system it affects (1). In epidemiological studies conducted in Turkey, the prevalence of MS was observed to be 0.4-1 in 1000 young adults. This is very similar to the global prevalence of MS (1-3). It is 2 times more common in women than in men (1). The average age of onset in Turkey is reportedly 30 years (1). In addition, several studies have revealed that the MS disease has a geographical distribution pattern (2,3). According to the studies, although various causes of the disease have been suggested, a definite cause has not been revealed (4,5). The general acceptance today is that there is a genetic predisposition in patients and that the disease occurs with the addition of environmental factors and other causes to this heredity (4,5).

MS patients are reported to come across several social, economic and psychological challenges both in Turkey and in the whole world (1,4-8). The loss of functionality caused by the progression of this disease leads to new problems and develops uncertainties and stress in the patient's self-perception, role performance, and expectations with their lives and relationships (6-8). According to a past study, since patients with MS deal with both the stress of daily life and the stress caused by the symptoms of the disease, stressful life events, and family problems occur more in these patients than in healthy individuals (6,7). Considering the lack of any definite treatment for this disease and accepting that a stress-free life is not possible with this condition, it has become important for patients to manage stressful situations that affect the disease course and to adapt to the disease by adopting effective coping mechanisms (6).

Considering the uncertainty related to this disease and its process, MS directly affects the quality of life of patients not only physically but also psychologically and socially (8). The treatment and postattack periods have a negative impact on the patient's work and social life as well as on their relatives (6,8). The psychological effects induced by MS can be classified as depression, stress, and anxiety, and from a social aspect, it includes problems such as family problems, job loss, stigmatization, the lack of access to social rights, and exclusion in social life (6-8). Although these problems are felt intensely from the first encounter with the disease until espousal, they reduce the quality of life by directly affecting the social functioning of the patients and their relationships with other people (7,8). Limitations caused by physical health problems of the patient, the increased dependence on others, the changing roles in the family, the loss of economic security, and the inability to attend or participate in social activities can affect the quality of life, as well as the social relationship between the patients and relatives (8).

The objective of this study was to qualitatively evaluate the challenges patients with MS face in a Turkish Public Hospital during its diagnosis and treatment and the societal aspects.

Materials and Methods

The sample was selected with maximum diversity in accordance with the purposeful sampling approach from patients visiting the outpatient clinic. The population of the study consisted 12 patients with MS (5 male and 7 females) of ages 19-50 years who were diagnosed with MS according to the McDonald 2017 Criteria and expanded disability status scale (EDSS) <5.5 (mild to moderate disability) who had been admitted to a public university medical school training and research hospital neurology department in Istanbul, Turkey. While an EDSS score of 5.5 included ambulation without aid, a patient with an EDSS score >6 (severe disability) needed one-sided help to walk. Various studies indicated that the quality of life of patients with MS is adversely affected in patients with EDSS score >6 than in those with EDSS score <5.5. Excluding severe cases might limit our findings' generalizability, in other words we can be biased as if MS patients don't have severe social challenges in life. Patients with cooperation difficulties, psychotic diseases, those who had an MS attack in the last 30 days, those who had received steroid therapy, and those with an active lesion visible on MRI were excluded from the study.

A mini questionnaire and a semistructured question guide were used in the study. The min-questionnaire included questions about their sociodemographic information and clinical status, while the semistructured question guide inquired about problems encountered while coping with MS, particularly concerning social life. Data was collected via an in-depth face-to-face interview. The interviews were audio-recorded after obtaining oral and written consent from the participants. Each interview lasted 30-55 min. A private room was used in the interviews to ensure that the participants felt safe and comfortable. All participants had previously met with their physicians and discussed their illnesses in similar rooms at the same polyclinic.

The audio records were deleted the same day after transcription. Two researchers were involved in each interview. The first researcher who conducted the interview and asked the questions. In cases where voice recording was not permitted, the second researcher was included in the interview with the participant's permission to take notes and observe the participant's body language and interview atmosphere.

Statistical Analysis

Each transcript was analyzed separately by two different researchers. The interviews were stopped when data saturation

was reached by the researchers and no new information could be obtained based on the responses of the participants. Themes and subthemes were determined after marking the codes with the consensus of the research team. A process of thematic and open coding was used to extract the themes. A coding manual was created to ensure intercoder reliability and coding consistency. Memos were used to obtain evidence of the decisions made to develop codes, sub-themes, and themes and then compared by the researchers. This method was adopted to ensure consistency, intercoder agreement, and trustworthiness, and to ascertain themes. This approach was followed exhaustively until saturation was reached and no new themes surfaced. Reliability and consistency were examined regularly through frequent comparisons of the transcripts. Validity was tested through the creation of a coding manual to ensure intercoder reliability and coding consistency.

Atlas-ti was used as the software program in the data analysis. In data analysis, the stages of data preparation (bracketing), phenomenological reduction (bracketing and phenomenological reduction), creative variation (imaginary variation), and revealing the essence of the experience (synthesizing meaning and essences) were used.

Ethical Considerations

Verbal informed consent was obtained from the participants before the interview began, and patients who did not give consent were not included in the study. Voice recordings were made during the interviews with the permission of the participants. The interviews were continued by asking different questions in some cases by replacing some of the items in the questionnaire. The participants were assured of the confidentiality and anonymity of their information so that they could respond freely. The participants were informed before the interview that they could not use their names and could use a nickname if they wished. The participant's data were protected in the voice recordings and analyses and not shared with any third party or institution. The data has been presented anonymously in this paper.

The study was approved by the Ethics Committee of Marmara University Faculty of Medicine (approval no: 09.2022-118,2, date: 10.10.2022) and complied with the principles of the Declaration of Helsinki. The participants were free to leave the study at any point of time and informed about the same before the start of the study.

Results

In this study, the experiences during the diagnosis and treatment periods and the burdens of the social life of 12 participants who were admitted to the neurology department of a public hospital in Istanbul, Turkey were investigated qualitatively. The sociodemographic features of the participants are listed in Table 1.

Of the 12 participants, 7 (58%) were females, and the age range of the participants was 19-50 years. One participant had no education, 1 had a postgraduate education (after a university degree), 1 was unemployed, 3 were housewives (not working), 9 were working, 1 was a student, and 6 (50%) had low income. No participants declared that they had a high income.

All participants, except one, had a core family, and all families lived in the urban area. While 6 participants had a history of febrile/rash illness, 1 had a relative with MS. In addition, 1 participant had essential thrombocytosis and another 1 had epilepsy.

Table 1. Distribution of participants according to their socio-demographic characteristics

	Sex	Age	Age of diagnosis	Educational status	Profession	Children	City they lived the longest	Marital status	Income
P1	Male	49	32	High school	Office worker	None	Mersin	Single	Low
P2	Female	48	35	Primary school	Housewife	3	Elazıg	Married	Low
P3	Female	20	13	High school	Retail worker	None	Samsun	Single	Low
P4	Female	36	15	High school	Housewife	1	Bursa	Married	Middle
P5	Female	41	35	Middle school	Housewife	3	Istanbul	Married	Middle
P6	Female	19	17	High school	Student	None	Istanbul	Single	Low
P7	Male	46	34	Primary school	Unemployed	2	Istanbul	Widower	Middle
P8	Male	43	29	Undergraduate	Industrial worker-(packaging)	2	Istanbul	Married	Low
P9	Female	23	16	Associate degree	Nurse	None	Istanbul	Single	Middle
P10	Female	32	27	Postgraduate	Banker	None	Istanbul	Single	Middle
P11	Male	40	37	High school	Industrial worker-(chemical painting)	2	Kocaeli	Married	Middle

The themes and subthemes of the interview results are presented in Table 2.

THEME A: EXPERIENCES DURING THE DIAGNOSIS AND TREATMENT PERIOD

Sub-theme A1: First Reactions to Diagnosis

Some participants stated that they had felt anxious and fearful when they were first diagnosed with MS. They explained that the reasons why they had felt so were mainly due to their thoughts and feelings including the fear of death, the possibility of the loss of function, and having no clue about what their future with the disease.

"I felt weird because I didn't know what the disease was like, I was scared."

(Participant 6, F, 19)

"I searched online how people who have MS disease live and I was shocked by how difficult it seemed at the time. There were many bad examples then I thought to myself "Am I going to end up this way? (laughs)."

(Participant 9, F, 23)

Sub-theme A2: Treatment

The participants admitted that the side effects and application methods of MS medication, which interfered with their daily functioning, made them hesitant to adhere to the treatment.

"…for example, I took my medication on the 17th of last month and will take it again this month on the same day but there will be some adjustments to my medication, so I am going to take it on the 25th this month. Obviously, it affects my social life when it is like this, affects my health, upsets me… (lost in tears)."

(Participant 3, F, 20)

"There were times when I couldn't reach a nurse (to administer medication). Drugs themselves also cause dizziness; I sometimes feel like the ground is shaking when I'm traveling in a car. Although I have blurry vision sometimes, I can't convince my doctor about it. After that, I didn't want to attend the visits and hadn't attended for a year."

(Participant 4, F, 36)

THEME B: ATTITUDE OF FAMILY MEMBERS AND THE SOCIAL CIRCLE

Sub-theme B1: Attitudes of Family Members

The participants declared that after being diagnosed with MS, their family members approached them with more consideration and tactfulness and also started to act more sensitively and with compassion then than before the diagnosis (Figure 1). While this situation was welcomed by some of the participants, considering it as a substantial indicator of the support extended by the family members, it was regarded unfavorably or perceived negatively by other participants, perceiving it as a trigger to the feeling of insufficiency and a sign of the family members' concerns (Figure 1).

"…They (parents) used to say 'It will clear up eventually, by God's will' as they had no idea about the extent of the disease and what it is. But still, they showed empathy toward me. They scold me when I want to work: 'It's not necessary, stay home'. They don't want me to get tired because of MS."

(Participant 7, M, 46)

"… (After the diagnosis) Everybody got worried. A state of fear and panic among everybody… They got more delicate, you know… Just as if one acts toward a child. It spoils you, how wouldn't it? (Laughs) Attention surely spoils you!"

(Participant 11, M, 40)

Table 2. Themes and sub-themes

Themes	Sub-themes (*illustrative quotes*)
A. Experiences during diagnosis and treatment period	A1- First reactions to diagnosis (*Am I going to end up this way?)* A2- Treatment (*Drugs themselves also cause dizziness)*
B. Attitude of family members and social circle	B1- Attitude of family members *("They got more delicate... Attention surely spoils you!")* B2- Attitude of social circle *("the people brought me unsalted bread or unsalted olives while I was taking cortisone…!")* B3- Stigmatization *("…You should not stare at me with hostility!")* B4- Thoughts about society's knowledge of the disease *("…They just view you like an immobile patient who can do nothing, who's bedridden…")*
C. Problems came across	C1- Problems came across in education*("...my internship would go to waste !")* C2- Problems came across in profession*("..my movements were restricted (at work)..!")* C3- Problems came across in social life *("Zumba activity. 'I can't come to that, it's too energetic'....It's affecting me badly!")* C4- Problems came across in romantic relations*("...when I tell a lady.... they turn away from me…!")*
D. Worries and coping mechanisms	D1- Individual worries*("… I thought that it (weakness on left side) would permanently stay with me all the time (Lost in tears)!")* D2- Worries about family*("....if there was a risk that our baby would inherit the same disease..... ")* D3-Religious coping, Self-soothing*(" ... it is a test from my God..... !")* D 4-Affirmation, Avoidance*("… it is tougher to be a cancer patient.....")*

Sub-theme B2: Attitude of the Social Circle

Most of the participants stated that they were not exposed to any kind of discrimination from their social circle and that they received extensive support, both materially and morally, after the diagnosis. Like the findings in Sub-theme 1, the participants diverged regarding their approach to the attitude shown to them, as it made some feel "backed up" and made some of them feel rather "insufficient." Certain participants abstained from sharing their feelings about their affliction related to MS from their social circle, but most showed no reluctance in expressing their problems, viewing it as a part of their support mechanism. Contrary to other participants, one participant expressed reproach when mentioning his social circle because of his feelings that no concern has been shown for him in his social circle.

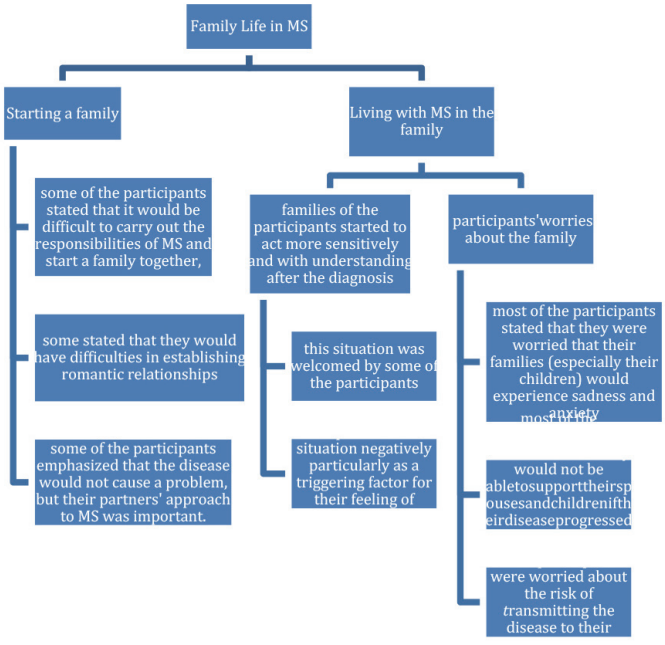

Figure 1. Figure summarizing the key findings of the study

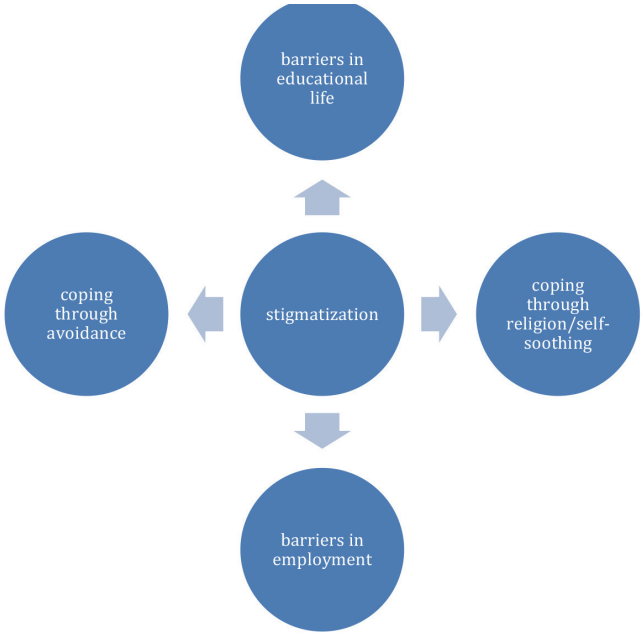

Figure 2. Family Life in MS
MS: Multiple sclerosis

"My boyfriend has a profound knowledge about MS, as his work is related to health insurance. I mean… He has supported me a lot. He has always stood by me, all the time after he came into my life."

(Participant 10, F, 32)

"I encountered more care and affection after the diagnosis. For instance, the people that brought me unsalted bread or unsalted olives while I was taking cortisone… (laughs) … (My schoolmates) They were all amazing! All of them came to the hospital and did what they could to entertain me. (joyfully) They flew balloons in front of my window, I can never forget that."

(Participant 4, F, 36)

Sub-theme B3: Stigmatization

It is observed that participants are exposed to stigmatization due to MS (Figure 2). This includes cases such as colleagues viewing the treatment process and the probability of attacks to occur in the workplace might be becoming an obstacle, or their diagnosis being disbelieved altogether (Figure 3). For example some colleagues thought that the participant was pretending to be sick to have frequent leaves at work (Figure 3).

The participants considered being disallowed from doing chores/daily housework by their close ones at home as a form of stigmatization, despite knowing that the underlying intentions were good (Figure 1). One participant stated that he faced stigmatization due to his gait.

"…People around me and my relatives always say, "don't tell her anything", "don't interfere with her" as some kind of protection thing, including my husband. It didn't exist before."

(Participant 5, F, 41)

"…You should not stare at me with hostility as if I'm the bogeyman. I mean, God forbid, this is not like a contagious disease after all."

(Participant 2, F, 48)

Sub-theme B4: Thoughts About Society's Knowledge of the Disease

Most participants believed that society is not adequately informed about MS. They expect society to obtain more reliable information, enabling them to recognize MS and the conditions caused by it. The participants contemplate that stigmatization can be reduced with an increase in the knowledge and awareness in the community about MS.

"…As far as I've seen, they're not that aware of MS in my surroundings. If I conducted research before, I got it, I would be more conscious

Figure 3. Living with MS at work
MS: Multiple sclerosis

about the disease. I would have taken care of myself more, but this all happened to me because I didn't know."

(Participant 2, F, 48)

"…I think they don't know at all. Because you explain it, and you see that they have no information by any means. They just view you like an immobile patient who can do nothing, who's bedridden…"

(Participant 9, F, 23)

THEME C: PROBLEMS CAME ACROSS

Sub-theme C1: Problems Encountered in Education

Participants whose education was continuing when they were diagnosed with MS indicated that the disease affected their educational life and that they struggled with keeping up with the school (Figure 2). Some participants said they could not proceed with their education or steer for the profession they desired.

"... Well, I was in high school during that time. I couldn't go to school for 3-4 months. Because the doctor said that I should rest after my discharge. I was also doing an internship at that time. My internship would go to waste… With that fear, my absence was more stressful. It (my education) got affected a little badly."

(Participant 9, F, 23)

"... for instance, I didn't want nursing school. Now I feel happy about my school but at the same time not really. Let me say I must feel content because of my illness. I wanted something related to aviation, to be honest. This is a disease that is not accepted in aviation, I feel bad about this for example."

(Participant 6, F, 19)

Sub-theme C2: Problems Encountered in the Profession

Most of the participants stated that MS had an adverse impact on their career, with many facing circumstances like rejection from a job and even employment termination (Figure 3); these concerns were negatively affected by this situation both financially and psychologically.

"... In fact, when the employers learned about this disease, they told me to get a medical report and do not come to work. I was also impressed by that. I didn't go to work for two or three months, and at one point they even considered firing me. Did they know MS better than me? They even said there was a disease that made him faint and fall down... Epilepsy???, So, I had financial difficulties; when you don't work, you don't get money at the beginning of the month ." (Participant 8, M, 43)

"... I mean, of course, when my movements were restricted (at work), you don't feel good when you can't do the action you wanted to do. Then the situation starts to become psychological. No wonder you feel angry toward yourself. And there is a difference between me 10-15 years ago and now needless to say. You are more energetic, nimbler, and faster. Of course, your elbowroom narrows. Thus, having a psychological effect on you. There's nothing else." (Participant 1, M, 49)

On the other hand, some of the participants argued that they received extensive support from their colleagues and that the busyness of business life worked positively for them (Figure 3).

"... The company protected us since it is a big well-known one. My responsibilities have been taken away (reduced). Otherwise, if you asked me, I would have fired directly. Is this why I hired you… The factory looked out for me. The protection taught us some things: "Don't say what I am, say what I'll become."

(Participant 11, M, 40)

Sub-theme C3: Problems Encountered in Social Life

While most of the participants stated that they experienced a limitation in their social life due to the presentation of their symptoms, some said that they continued their normal lives as much as possible by adjusting their social plans such that they would not trigger attacks/relapses by trying to adapt to their illness.

"... Only the first two months were too hard. Other than that, I go to the cinema and wander around with my daughter. The only thing that bothers me is the three months of summer, for example, I cannot go out much because of the heat. My husband takes me out with the car in the evenings. For instance, going out for dinner or shopping, I can do them only in the evening. I can't do anything in the daytime. Heat is my only nuisance…"

(Participant 5, F, 41)

"I kept doing everything normally, so I did not encounter any difficulties. There is just a situation like this; For example, we have a

group. An activity will be done. I tell them this game is not suitable for me because I have such a disease. For example, what can I say about the Zumba activity. 'I can't come to that, it's too energetic." I don't need to raise my body temperature too much. It's affecting me badly. I say there is such a situation."

(Participant 10, F, 32)

Sub-theme C4: Problems That Came Across in Romantic Relations

Some of the participants stated that acknowledging the difficulty in carrying out the responsibilities of MS and starting a family together made it difficult to establish romantic relationships (Figure 1). However, some of the participants emphasized that the disease would not cause a problem, but their partners' approach to MS was important (Figure 1).

"...I mean it feels like if the other party had searched or knew (the disease) it might work; my wife is a primary school drop-out, she didn't know anything about the disease. "If I didn't tell her about my disease, then it would have caused problems in our marriage."

(Participant 8, M, 43)

"... Now, for example, I would not want to marry a woman with MS. Because the child will most likely be born with MS. Now, I don't want my child to go through what I went through. So, for example, when I tell a lady, I'm like this, they turn away from me… "

(Participant 1, M, 49)

THEME D: WORRIES AND COPING MECHANISMS

Sub-theme D1: Individual Worries

Participants admitted that they had been feeling anxious that their disease might progress in an unfavorable manner, ultimately resulting in the loss of function, causing them to be "in need of someone." They also mentioned that their anxieties tended to increase when they saw some other patients with MS with a more severe form of the disease.

"… (People had told me) 'I have a friend, relative with MS disease and they don't walk, hear… Had a disease attack now he/she cannot see, have troubles on his/her left side'. I also had a disease episode that affected mainly my left side and I kept remembering what they had been saying… I thought that it (weakness on left side) would permanently stay with me all the time (Lost in tears). When I have an appointment at the doctor's office, I usually prefer it early in the morning so it would not be likely for me to see elderly people with advanced diseases. I feel like I will end up like them too in the future when I see them."

(Participant 3, F, 20)

Sub-theme D2: Worries About Family

Most of the participants stated that they were worried that their families (especially their children) would experience sadness and anxiety and that they would not be able to support their spouses and children if their disease progressed. In addition, they were worried about the risk of transmitting the disease to their children (Figure 1). A participant also mentioned that they worried about becoming a burden to their family.

"… I had not wanted to have a baby for 6 years… Later, we decided to have a baby. At that time, my husband told me that he was concerned if there was a risk that our baby would inherit the same disease, if anything bad would happen to him/her."

(Participant 4, F, 36)

"… I used to cry a lot… when I see my mother or my children. It used to affect my children a lot when I cried. I felt rebellious when I was diagnosed. I had a 1-year-old child, and I wished that I hadn't had a baby in the first place."

(Participant 2, F, 48)

Sub-theme D3: Religious Coping/Self-soothing

Many participants stated that they adopted religion and religious motives as their coping mechanism throughout their disease course (Figure 2). They explained that the use of this approach helped them comprehend the meaning of their disease and express their feelings. The participants thought that the situation in which they lived was too much for their essence and tried to accept the disease by glorifying the cause of the disease.

"It is what God has given… what can I do? I suppose He's testing me."

(Participant 1, M, 49)

"I comfort myself by thinking it is a test from my God. I wish for the best for myself."

(Participant 7, M, 46)

"…Coming from God… it has come to us too."

(Participant 12, M, 50)

Sub-theme D4: Affirmation and Avoidance

Affirmation: The participants tried to accept their disease by disregarding it and convincing themselves that it is not very severe in comparison with other diseases/medical conditions (Figure 2).

"… it is tougher to be a cancer patient. I mean, think about the worse diseases. The course of the disease could be worse."

(Participant 5, F, 41)

Avoidance: Some participants tried to cope with their situation by avoiding negative thoughts or neglecting the fact that they had a medical condition (Figure 2).

"I don't want to put myself in such a negative mood. When negative thoughts/feelings occur, I think to myself '… there's nothing bad,

you are over-thinking, don't mind it, let's do this/that (some activity)'.

(Participant 3, F, 20)

"… I went to work, if I stayed home I would be constantly thinking like 'What's going to happen next?' Will it cause me harm? Will I have a disease attack?' whether I like it or not. While I was working, I wouldn't think about it, so I worked."

(Participant 8, M, 43)

Discussion

This study investigated how individuals diagnosed with MS spent their diagnosis and treatment period what sort of socio-economic and psychological challenges they faced in their family life, social life, educational, and professional life during this period, and their coping mechanisms. In addition to the trust ensured by the clinical environment maintained during the interviews, the participant's trust in the doctors and clinical team, who have been following them up for years, provided the researchers with the ability to conduct in-depth interviews. Although the experiences of the participants varied based on the sociocultural structures of their families, social circles, and their perspectives, some common patterns were detected within the examined problems. In harmony with its purpose, the experiences of individuals diagnosed with MS regarding the diagnosis and treatment processes and the problems experienced in social life were examined in-depth by this study and approached in a multidimensional manner.

In connection with the limitation of the public's knowledge and awareness about MS, the participants were left alone with severe internal problems because they did not have any information about the disease at the time of their diagnosis. This could also have been raised from the impressions gained from the lives of patients with MS they had come across. The thoughts underlying the fears and anxieties felt as the initial reactions after the diagnosis were mostly related to the probable decline in functionality and quality of life, uncertainty about the future, the idea of approaching death and leaving family members behind. In a similar study conducted in Greece, most patients diagnosed with MS stated that the most common emotion they had was fear because of the uncertainty of what MS would bring to them in the future (9). In another similar study conducted in Turkey, the participants were asked, "How did you react after you learned the diagnosis?" (8) to which they mostly replied with "I cried,""I could not accept, I was very upset," "I was very surprised," and "I was afraid of what would happen," indicating fear, shock, and uncertainty (8).

In our study, all the participants lived in metropolitan cities during the diagnosis and treatment process and none reported any difficulties accessing the routine treatment. All participants were committed to their treatment. However, the drugs were required to be used continuously and the related side-effects of these drugs were an important reason for the periodic disruption of treatments. In a study conducted in Iran (10), some of the participants stated that they stopped the drug treatment because they were tired of the long treatment process and wanted to continue with their normal lives; furthermore, some patients turned to herbal treatments and waited for complete recovery. In this past study, the families and social circles of the patients with MS seemed to exhibit supportive behavior and made efforts to ease the participants' lives (10). Although several participants agreed with this, they mentioned that behavior changes after the diagnosis may lead a person to feel insecure and incompetent. They also mentioned that feelings of anxiety displayed by family members were disturbing at times (10). In another study conducted in Norway, a similar distinction was noted among the participants' approach to their family members' actions (11). It was also found that pampering patients could lead them to inflict a discriminatory manner even when the intentions were good, which was recognized as a derivative of stigmatization (11).

In a similar study (12), patients wanted to learn more about the disease before taking any action as MS was a completely new disease for them at the time of their diagnosis, as verified by many participants stating misperceptions about the disease before the diagnosis. They stated that the reason for the misperceptions about MS was due to the lack of knowledge and negative attitudes of individuals in society toward patients with MS (12).

In the present study, the limited knowledge of patients, their relatives, and society about MS was striking. It is therefore evident that the level of knowledge shapes the manner of approach to patients by their social environment. Moreover, wrong and incomplete beliefs about the course and effects of the disease may cause experiences that are negatively evaluated by the participants, such as stigmatization and discrimination in the workplace (12,13). The process of obtaining information usually proceeds through the efforts of the patients themselves; however, this process may not always occur through reliable sources. For some of the participants, obtaining information about the disease course was perceived as anxiety-provoking, which undermined the process of obtaining information.

The participants thought that increased knowledge and awareness of the community about MS could prevent acts of stigmatization from occurring. Similar to that in previous studies, here, many participants stated that the community did not have sufficient knowledge about MS. The participants hoped that the community would learn and understand MS and related symptoms.

Similar to that in the literature, the present participants also faced various problems in their educational life (14). Physical and mental difficulties stemming from MS led to issues such

as absenteeism or a downfall in academic performance throughout patients' education, which affected their career choices. In a similar research (14), patients with childhood-onset MS had difficulty adapting to school life, and they exhibited a decline in their academic performance, which negatively affected their education.

Unemployment is an important drawback for people diagnosed with MS. Some researchers suggest that this issue stems from personal factors such as disability, tiredness, or a lack of education, while others have linked this issue to societal causes such as negative attitudes toward the patients or a lack of physical amenities (12-16).

In parallel with the literature reports, this research exhibited that participants faced disruptions in their occupational and educational lives due to the inability caused by MS and due to the process of treatment. Some participants who faced the threat of termination of employment due to MS or had encountered discrimination in the recruitment processes faced financial losses. On the contrary, the accounts of participants who had received support from their employers or co-workers constituted a crucial sample that displayed consideration of the disease burdens in the workplace, resulting in a positive impact on the patient's quality of life.

Another study demonstrated that social support could be highly beneficial for patients to develop skills regarding coping with health problems (15). A social circle that is aware of the social, physical, and mental problems of MS can help the patient get relief in terms of both apprehension and the burden of the disease.

According to a past study, the fear caused by the uncertainty of the prognosis was identified as a significant factor that could have a stronger negative impact on the quality of life than the disease itself (12). The anxiety levels of patients can be ameliorated by having adequate knowledge about the prognosis of MS. It is therefore speculated that informative sessions following outpatient controls can assist in this regard. Counseling services and therapeutic interventions offered by healthcare professionals can be beneficial in maintaining the patients' mental well-being.

It is remarkable that most participants described seeking information about MS and seeing other patients with worse clinical status as triggering factors for anxiety. The participants stated that these concerns affected their mood chronically. The probability of symptoms progressing raised concerns in the patients, built upon the thoughts of losing function and affecting the family members. It was concluded by a population-based study that people with MS scored significantly higher in anxiety and depression scales, on the grounds of the physical symptoms of MS and its effect on their families (16). It is therefore attested that MS can paradoxically exert both negative and positive effects on family life based on emotional stress, separation, economic hardship, fear of abandonment, or familial relationships becoming more profound (17).

Participants described living with MS as a situation that created an emotional burden. The commonly used mechanisms to cope with this burden included perceiving the disease as a divine outcome, either ignoring the symptoms totally or underestimating its extent, making efforts to recuperate so as not to burden others, and engaging in distracting activities. Particularly, in the early stages of MS, avoidance was found to be often applied as a coping mechanism. Emotional support of the social circle and information about physical activity were identified as being crucial for orientating into a life with MS (18). Notably, coping mechanisms differed among patients in relation to their familial structures and sociocultural features (18,19). Another study identified "denial" as the most sighted coping mechanism (19).

Study Limitations

Considering the qualitative nature of this study, the results cannot be generalized to all populations. The participants were selected from patients with MS who were admitted to neurology outpatient clinics and were not in the attack period. Patients with an EDSS score <5.5 were included in this study. Therefore, the participants were mobile, could maintain their daily lives, and did not have permanent functional loss. The findings related to patients with severe functional loss were not included in our study. Excluding severe cases may have limited our findings' generalizability, in other words, it adds bias as if patients with MS do not have severe social challenges in life. The veracity that the study was conducted at a single center with patients who did not experience any limitations in access to treatment can be shown as a limitation.

Conclusion

The results indicated that participants may experience problems such as stigmatization, anxiety, and discrimination due to the insufficient level of knowledge about MS. Official sanctions applied against discrimination in schools and workplaces may prevent patients from losing their social rights and experiencing a downfall in their quality of life. Practical interventions, such as community education programs or patient-centered care models, should be developed and implemented.

Researchers believe that conducting population-based cross-sectional quantitative studies in larger samples and with variations in the loss of function may produce results that could be generalized to the population. Past studies including those on people with severe MS can be recommended. New quantitative studies developing scales such as quantitatively measuring stigma in patients with MS or perceived empathy in patients with MS can be recommended after our qualitative

study or conducting prospective longitudinal studies can also be recommended.

Further studies inquiring about implementations by health authorities for patients and their relatives might be needed. The development of better health education policies by health authorities with the aim of targeting the population is also recommended.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of Marmara University Faculty of Medicine (approval no: 09.2022 -1182, date: 10.10.2022).

Informed Consent: The participants were free to leave the study at any point of time and informed about the same before the start of the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.O.G., B.M.S., A.E.K., A.U., M.N.K., D.I.G., G.S., Concept: A.S.K., S.H., M.T.B., M.K., Design: A.S.K., S.H., M.T.B., M.K., K.A., Data Collection or Processing: B.O.G., B.M.S., A.E.K., A.U., M.N.K., Analysis or Interpretation: A.S.K., S.H., M.T.B., B.O.G., B.M.S., A.E.K., A.U., M.N.K., M.K., Literature Search: A.S.K., M.T.B., B.O.G., B.M.S., A.E.K., A.U., M.N.K., Writing: A.S.K., M.T.B., B.O.G., B.M.S., A.E.K., A.U., M.N.K., M.K.

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RESEARCH ARTICLE

Correlation of Breastfeeding with Disease Development and Progression in Patients with Multiple Sclerosis

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Abstract

Objective: Breastfeeding during infancy has been shown to be protective against autoimmune diseases. This study aimed to determine the correlation between breastfeeding during infancy and disease development and progression in patients with multiple sclerosis (MS).

Materials and Methods: This study included 180 participants, comprising 90 patients with MS and a control group of 90 healthy individuals. Demographic characteristics, duration of disease, age of onset, number of attacks, annual relapse rate, expanded disability status scale (EDSS) scores, and duration of breastfeeding of patients with MS were recorded.

Results: No significant difference was found between the two groups; the duration of breastfeeding was 13.67±9 months in the MS group and 14.3±9.4 months in the control group. Furthermore, there was no statistically significant difference in age of onset, annual relapse rate, number of attacks, or EDSS values between groups with ≤4 months and >4 months of breastfeeding and between ≤6 months and >6 months of breastfeeding.

Conclusion: According to the results of this study, breastfeeding duration was not significantly correlated with disease development, age of onset, or disease progression in patients with MS. However, further studies with a larger sample group are required to validate the findings.

Keywords: Breastfeeding, multiple sclerosis, disease progression, attack

Introduction

Multiple sclerosis (MS) is a chronic central nervous system disease marked by demyelination and axonal degeneration. The disease exhibits heterogeneity in symptoms, disease course, and outcomes (1). MS is a global problem, and non-traumatic neurological disability is a major cause of disability among young adults. The prevalence of the disease is increasing, and 2.8 million people worldwide are estimated to be living with MS (approximately 900,000 in the United States of America) (2-4). In relapsing MS, women are affected almost three times more frequently than men, and the average age of onset is approximately 30 years (4-6). MS phenotypes are defined as relapsing-remitting MS (RRMS), primary progressive MS (PPMS), active secondary progressive MS (SPMS), and non-relapsing SPMS (7). RRMS is the most common phenotype, affecting approximately 85% of patients with MS. This condition is characterized by alternating episodes of neurological dysfunction, known as relapses, and episodes of relative clinical stability without new neurological symptoms, known as remissions (8).

Diverse environmental and genetic factors are involved in the etiology of MS. Environmental factors such as age, sex, smoking, sunlight exposure, vitamin D levels, race, and climate are known to play a significant role in the development of MS (9). Diet is a crucial environmental exposure during early development (10). Breast milk contains various immunological, biochemical, and cellular components that can considerably alter infection susceptibility and neonatal immunity (11). The correlation between breastfeeding and MS has been examined in several studies so far, but the results are conflicting (12,13). In recent studies, breastfeeding for at least 4 months has been reported to be a protective factor against the risk of MS development, but the role of breastfeeding in determining the risk of MS is yet to be established (14). No previous studies have shown a

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correlation between the duration of breastfeeding and disease progression and the age of onset in patients with MS. Therefore, this study aims to investigate the correlation between breastfeeding during infancy and disease development and progression in patients with MS.

Materials and Methods

A total of 90 patients with MS who were followed up in the MS outpatient clinic of the Neurology Department of Ataturk University Faculty of Medicine between April 1st, 2020, and April 1st, 2021, whose breastfeeding periods were determined, and who met the 2010 McDonald MS diagnostic criteria were included in the study. As a control group, 90 individuals who applied to the outpatient clinic of the Department of Neurology of Ataturk University Faculty of Medicine with the complaint of headache, whose cranial magnetic resonance imaging was normal, and whose age and sex were matched were included in the study. The duration of breastfeeding was learned by contacting the patients' mothers. Individuals who were under the age of 18, whose mothers were not alive, and who had autoimmune diseases and other systemic diseases were excluded from the study. The demographic characteristics and expanded disability status scale (EDSS) scores of the patients with MS were determined.

The approval of the Clinical Research Ethics Committee of the Ataturk University Faculty of Medicine was obtained before commencing the study (decision no: 02, date: 26.03.2020). Informed consent was obtained from the participants.

Statistical Analysis

Means and standard deviations for normally distributed data and medians with minimum and maximum values for non-normally distributed data were used to calculate the summary statistics for all participants. The D'Agostino-Pearson test was used to assess normality. The χ^2 test was used to evaluate categorical variables that were nominal. To compare continuous variables with a normal distribution between the two groups, the Student's t-test was used. The Mann-Whitney U test was used to compare non-normally distributed data, whereas the Spearman rank correlation was used to determine the correlation between non-parametric variables. The Spearman rank correlation was used to ascertain the correlation between non-parametric variables. Two-sided p-values of <0.05 were used to indicate statistical significance. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS 20.0) for the Windows version.

Results

Of the people with MS, 71.1% were women and 28.9% were men. The mean disease duration in the MS group was 8.05±5.5 years. The mean EDSS score was 2.13±1.76. Table 1 presents the demographic and clinical characteristics of both the MS and control groups. The duration of breastfeeding was recorded as 13.67±9 months in the MS group and 14.3±9.4 months in the control group, with no statistically significant difference between the two groups (p>0.05). Furthermore, no significant difference was observed in the duration of breastfeeding between men and women with MS (p>0.05). In addition, there was no statistically significant difference in breastfeeding duration between patients with RRMS and those with progressive MS (SPMS and PPMS) (p>0.05) (Table 2). Moreover, our analysis showed no significant correlation between the duration of breastfeeding and EDSS scores, age of onset, number of relapses, or annual relapse rate (Table 3). The patients with MS and the control group were classified based on the duration of breastfeeding: ≤4 months, >4 months but ≤6 months, and >6 months. The patients with MS did not differ significantly from the controls. In addition, there were no statistically significant differences in EDSS score, age at onset, annual relapse rate, or number of attacks between patients with MS breastfed for ≤4 months and >4 months and between those breastfed for ≤6 months and >6 months (p>0.05) (Table 4).

Discussion

In our study, although the duration of breastfeeding was lower in the MS group than in the control group, the difference was not significant. The duration of breastfeeding was not correlated with the patients' EDSS scores, age of disease onset, number of attacks, or annual relapse rate. Patients with MS and the control group were categorized into groups based on their breastfeeding duration as ≤4 months and >4 months and ≤6 months and >6 months. No statistically significant difference was observed between the MS and control groups in terms of these durations and age of disease onset, annual attack rate, number of attacks, or EDSS values.

Numerous studies have been conducted on environmental risk factors in MS, indicating the significance of environmental effects during infancy and youth. Diet, especially breast milk, is a crucial environmental exposure during early development (14,15). Breast milk, which is a rich source of immunoglobulin, lactoferrin, lysozyme, cytokine, and several other immunologic factors, provides the infant with active and passive immunity. Leukocytes account for 2% of healthy breast milk (16). Leukocytes primarily provide active immunity and support the development of immunity in infants (17). Furthermore, miRNAs, which are present at high levels in breast milk, play a role in promoting the survival of leukocytes in the infant's gastrointestinal tract and might possess immune-protective functions (18). Better Th1 responses have been noted in children breastfed earlier than those breastfed with baby formulas exhibiting immunomodulatory effects (19). Different gut microbiota and stronger memory T-cells and Th17 cell

populations have been reported to develop in breastfed infants compared with those who were bottle-fed (20). Therefore, the World Health Organization recommends that infants be exclusively breastfed for the first 6 months after birth and that partial breastfeeding be continued until at least 2 years of age (21).

Previous studies have identified breastfeeding as a protective factor against bronchial asthma, atopic dermatitis, type 1 diabetes mellitus, and Crohn's disease (22-24). Breastfeeding duration has been shown to exert a gradual effect on certain diseases, such as celiac disease. Breastfeeding for >6 months has been documented to have a protective effect (25,26).

Table 1. Clinical and demographic characteristics of patients with MS and the control group

	MS n=90 mean ± SD; median (min-max)/n(%)	Control n=90 mean ± SD; median (min-max)/n(%)	p-value
Age (year)			
Women	35.76±9; 36 (20-56)	35.78±9; 36 (20-56)	0.76*
Men	35.15±8.2; 35 (21-53)	35.15±8.2; 35 (22-53)	0.76*
Total	35.58±8.7; 36 (20-56)	35.60±8.7; 36 (20-56)	0.99*
Sex			
Female	64 (71.1%)	64 (71.1%)	
Male	26 (28.9%)	26 (28.9%)	
Duration of breastfeeding (month)	13.67±9; 12 (0-48)	14.3±9.4; (0-36)	0.57**
Age of onset (year)	27.51±8.5; (10-50)	–	–
Duration of the disease (year)	8.05±5.5; 7 (1-24)	–	–
Total number of attacks	3.62±2.3; 3 (1-10)	–	
Annual relapse rate	0.57±0.35; 0.5 (0.1-2)	–	–
EDSS	2.13±1.76; 1.75 (0-7)		
Type of disease			
RRMS	77 (85.6%)		
SPMS	11 (12.2%)		
PPMS	2 (2.2%)		
Immunomodulatory medications			
Interferon beta 1a	26 (28.9%)		
Interferon beta 1b	7 (7.8%)		
Glatiramer acetate	7 (7.8%)		
Fingolimod	24 (26.7%)		
Teriflunamide	10 (11.1%)		
Dimethyl fumarate	6 (6.7%)		
Natalizumab	2 (2.2%)		
Ocrelizumab	8 (8.9%)		

*Student's t-test, **Mann-Whitney U test, EDSS: Expanded disability status scale, SD: Standard deviation, MS: Multiple sclerosis, RRMS: Relapsing-remitting MS, PPMS: Primary progressive MS, SPMS: Secondary progressive MS

Table 2. Correlation between sex and type of disease and breastfeeding in patients with MS

	Duration of breastfeeding (months) Mean ± SD; median (min-max)	p-value
Gender		
Male	14.46±8.9; 12 (0-36)	0.52**
Female	13.35±9.2; 12 (0-48)	
Type of disease		
RRMS	13.46±8.86; 12 (0-48)	0.59**
PMS (SPMS + PPMS)	14.92±10.6; 12 (0-30)	

**Mann-Whitney U test, SD: Standard deviation, MS: Multiple sclerosis, RRMS: Relapsing-remitting MS, PPMS: Primary progressive MS, SPMS: Secondary progressive MS

Table 3. Correlation of the duration of breastfeeding with EDSS, age of onset of MS, number of attacks, and annual attack rate in patients with MS

		EDSS	Age of onset of MS, year	Duration of MS, year	Number of attacks	Annual relapse rate
Duration of breastfeeding	r	0.082	-0.081	0.083	0.182	0.037
	p	0.442	0.443	0.436	0.085	0.727

EDSS: Expanded disability status scale, MS: Multiple sclerosis

Table 4. Clinical findings in patients with MS according to breastfeeding durations of ≤4 months and >4 months and ≤6 months and >6 months

	Breastfeeding					
	≤4 months	>4 months	p-value	≤6 months	>6 months	p-value
Healthy control n(%)	29 (24.4%)	61 (75.6%)	0.515*	22 (46.3%)	68 (53.7%)	0.19*
MS n(%)	25 (16.7%)	65 (83.3%)		15 (51.6%)	75 (48.4%)	
Age of onset	25.46±7.3; 23 (16-46)	27.9±9.1; 27 (10-50)	0.939**	25.46±7.3; 23 (16-46)	27.9±9.1; 27 (10-50)	0.28**
EDSS	2.1±2.09; 1 (0-7)	2.14±1.7; 2 (0-7)	0.913**	2.1±2.09; 1 (0-7)	2.14±1.7; 2 (0-7)	0.62**
Annual relapse rate (3)	0.54±0.3; 0.45 (0.1-1.2)	0.58±0.3; 0.5 (0.1-2)	0.967**	0.54±0.3; 0.45 (0.1-1.2)	0.58±0.3; 0.5 (0.1-2)	0.73**
Number of attacks	3.8±2.7; 3 (1-10)	3.57±2.2; 3 (1-10)	0.807**	3.8±2.7; 3 (1-10)	3.57±2.2; 3 (1-10)	0.83**

*Chi-square, **Mann-Whitney U test, EDSS: Expanded disability status scale, MS: Multiple sclerosis

Research has established a positive correlation between the duration of breastfeeding and the development of white matter pathways from 10 months to 4 years of age (27). In a separate study, breastfed children were found to experience a prolonged period of white matter development between 16 months and 2 years of age, resulting in an overall increase in detectable myelin by the age of 2 years, which continues throughout childhood (28). Consistent with the research indicating that breastfeeding impacts myelination timing, children with a longer breastfeeding experience showed increased encephalon volume, cortical thickness, and white matter volume (27,29). Several studies have explored the association between breastfeeding and MS, but the findings have been conflicting. In their study, Spencely and Dick (12) failed to observe a correlation between breastfeeding and the risk of developing MS. In another study, the researchers compared patients with MS who were breastfed for 8.4 months with the control group who were breastfed for 12.5 months. The study revealed a correlation between extended breastfeeding and a reduced risk of MS (13). Breastfeeding for at least 4 months was determined to be related to a reduced risk of developing MS by Conradi et al. (14). Human milk is believed to play a protective role in the pathogenesis of MS owing to its ability to protect against toxins and pathogens as well as modulate the immune response (30,31). Furthermore, breastfeeding may be linked to the ability to promote the development of immunity, including the production of interleukin-10 and immunomodulatory effects with antiinflammatory transforming growth factor-β (27,32). The present study compared the duration of breastfeeding between patients with MS and a healthy control group, and no significant difference was observed. The association between breastfeeding duration and the risk of MS is currently a debatable topic (33). In a case-control study, Ragnedda et al. (34) reported that men who were breastfed for <4 months had an increased risk of MS. Brenton et al. (35) conducted a study that demonstrated a significant correlation between not breastfeeding and the likelihood of developing pediatric-onset MS. Nevertheless, the researchers did not observe a correlation with the duration of breastfeeding. Our study compared patients with MS and a healthy control group with breastfeeding durations of ≤4 months and >4 months and ≤6 months and >6 months but found no significant difference between them. No studies have so far examined the correlation between breastfeeding duration and MS disease progression or number of attacks. Our study found that the duration of breastfeeding was not correlated with EDSS scores, age of onset, number of attacks, or annual relapse rate of patients with MS. To the best of our knowledge, this is the first study on this topic.

Study Limitations

The limitations of our study include the relatively small sample size and the fact that the duration of breastfeeding was obtained from subjective data based on self-reporting.

Conclusion

In conclusion, we report for the first time the absence of a significant association between the duration of breastfeeding in infancy and disease development, age of disease onset, annual attack rate, and disease progression in patients with MS. We recommend conducting the study with a larger sample group.

Ethics

Ethics Committee Approval: The approval of the Clinical Research Ethics Committee of the Ataturk University Faculty of Medicine was obtained before commencing the study (decision no: 02, date: 26.03.2020).

Informed Consent: Informed consent was obtained from the participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: N.B., Y.D., F.D., F.Ş., Concept: N.B., Y.D., F.D., F.Ş., Design: N.B., Y.D., F.D., F.Ş., Data Collection or Processing: N.B., Y.D., F.D., F.Ş., Analysis or Interpretation: N.B., Y.D., F.D., F.Ş., Literature Search: N.B., Y.D., F.D., F.Ş., Writing: N.B., Y.D., F.D., F.Ş.

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CASE REPORT

Area Postrema Syndrome: A Rare Presentation of Neurosarcoidosis

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Abstract

This case report describes a rare occurrence of neurosarcoidosis presenting as area postrema syndrome, marked by severe nausea and vomiting. A woman in her 30s developed persistent symptoms following a cesarean section. Diagnostic investigations, including magnetic resonance imaging and cerebrospinal fluid analysis, confirmed the diagnosis of neurosarcoidosis. Treatment with prednisolone resulted in substantial symptom relief. This case emphasizes the need to consider neurosarcoidosis in the differential diagnosis of unexplained gastrointestinal symptoms and highlights the diagnostic challenges associated with such atypical presentations.

Keywords: Neurosarcoidosis, area postrema syndrome, granulomatous inflammation, cranial neuropathies, magnetic resonance imaging

Introduction

Neurosarcoidosis, a form of sarcoidosis involving the nervous system, occurs in 5-10% of sarcoidosis cases and presents with a range of neurological symptoms caused by granulomatous inflammation. It can involve various regions of the nervous system, including the meninges, brain, cranial nerves, spinal cord, and peripheral nerves, resulting in diverse clinical presentations (1). Among these, cranial neuropathy is the most common manifestation, affecting 50-70% of individuals with neurosarcoidosis, with the optic nerves being the most frequently involved (2).

The area postrema, situated on the dorsal surface of the medulla oblongata, plays a crucial role in regulating the vomiting reflex. Involvement of this structure in neurosarcoidosis can result in a rare clinical entity known as area postrema syndrome, characterized by persistent nausea and vomiting (3). Given its rarity, this manifestation necessitates heightened clinical awareness and comprehensive evaluation in patients with unexplained nausea and vomiting, as it presents notable diagnostic challenges (4).

This case report highlights the uncommon presentation of area postrema syndrome within the neurosarcoidosis spectrum, emphasizing its consideration in the differential diagnosis of refractory nausea and vomiting.

Case Report

A woman in her 30s presented to our clinic with persistent nausea, vomiting, and fatigue that had persisted for 3 years. These symptoms began following a cesarean section and were marked by intermittent exacerbations without complete resolution. One year prior to her visit, she experienced a single episode of status epilepticus. During her admission to intensive care, magnetic resonance imaging (MRI) revealed hyperintensity in the right and left medial temporal lobes (Figure 1), raising suspicion for encephalitis. Cerebrospinal fluid (CSF) analysis at the time showed elevated protein levels at 244 mg/dL, with no other abnormalities or malignant cells detected.

On examination in our clinic, the patient appeared frail but was alert, cooperative, and oriented. Neurological assessment revealed horizontal and vertical nystagmus, while other cranial nerve functions remained intact. Muscle strength was preserved; however, she was unable to walk unassisted due to severe ataxia. Deep tendon reflexes were significantly brisk, with positive clonus and bilateral extensor plantar responses. MRI showed mild hyperintense lesions in the brainstem, right medial temporal lobe, and right cerebellum, indicative of neuroinflammatory processes. Post-contrast imaging revealed symmetric nodular-subpial enhancement along the cervical spinal cord, as well as involvement of the supratentorial meninges, brainstem, and cerebellum. These findings, consistent

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with neurosarcoidosis, reflect granulomatous inflammation (Figure 2).

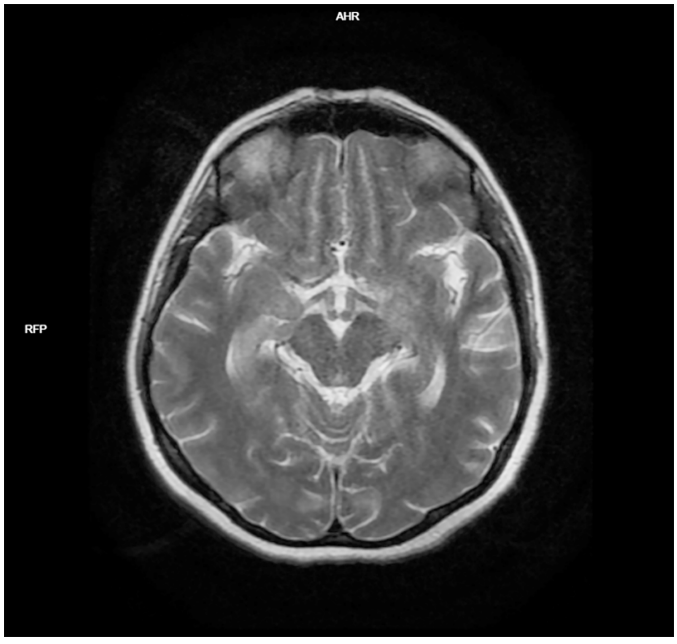

Figure 1. Axial T2-weighted MRI taken with a 1.5-T scanner, showing hyperintensity in the right and left medial temporal lobes, consistent with neurosarcoidosis

MRI: Magnetic resonance imaging

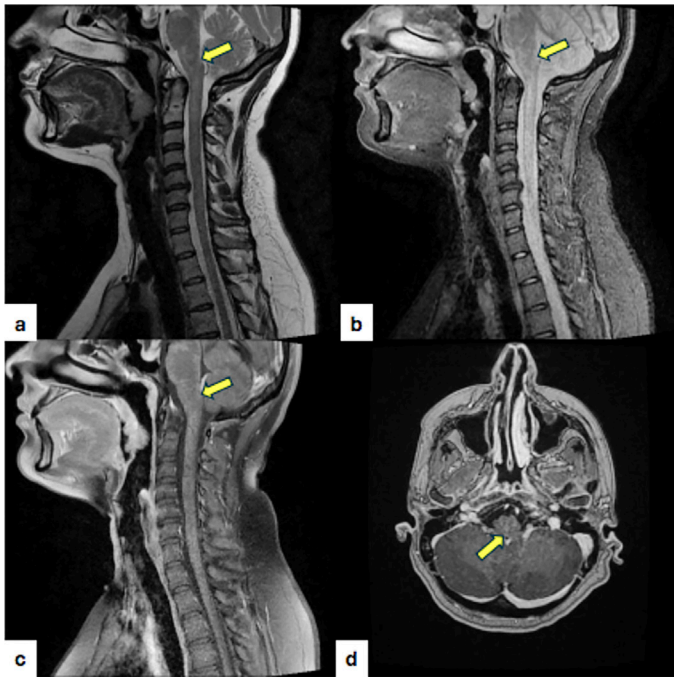

Figure 2. Sagittal T2 (a), short tau inversion recovery (b), post-contrast sagittal T1 (c), and axial T1 (d) MRI obtained with a 1.5-T scanner. These images reveal symmetric nodular-subpial enhancement along the cervical spine, as well as supratentorial meningeal and brainstem-cerebellum involvement, typical of neurosarcoidosis

MRI: Magnetic resonance imaging

Serum angiotensin-converting enzyme (ACE) levels were elevated at 82 U/L (normal range, 8-52 U/L), and 24-h urinary calcium was also increased. Repeat CSF analysis revealed a protein level of 177 mg/dL, with no cellular abnormalities. Tests for oligoclonal bands, serum NMO-IgG, and anti-MOG antibodies were negative, as was the autoimmune encephalitis panel. Chest computed tomography (CT) identified multiple lymphadenopathies in the mediastinal, subcarinal, bilateral hilar, and intrapulmonary regions, with the largest measuring 16 mm. Additionally, parenchymal nodules with a perilymphatic distribution, a hallmark of systemic sarcoidosis, were observed. These systemic findings, combined with the neurological features, supported the diagnosis of neurosarcoidosis (Figure 3). The differential diagnosis initially considered other potential causes, including encephalitis and demyelinating diseases such as multiple sclerosis and neuromyelitis optica spectrum disorder (NMOSD). The diagnosis of neurosarcoidosis was strongly supported by the presence of systemic sarcoidosis features, such as lymphadenopathy and parenchymal nodules on chest CT, contrast-enhanced MRI findings, and elevated ACE levels. A lymph node biopsy confirmed the diagnosis. Treatment began with prednisone at 1 mg/kg daily, in coordination with the pulmonology team to address both neurosarcoidosis and systemic sarcoidosis. Later, mycophenolate mofetil (2 × 1000 mg daily) was added. Significant improvement was noted within a week of prednisone treatment, with marked reduction in nausea and vomiting and improved ataxia, enabling the patient to walk with support. She remains under close follow-up for treatment response and medication adjustments (Figure 4).

Discussion

Sarcoidosis, an immune-mediated disease characterized by granulomatous inflammation, can affect multiple systems, with the lungs, skin, eyes, liver, lymph nodes, and nervous system being commonly involved in 5-10% of cases. Neurosarcoidosis can lead to significant morbidity and has been identified in up to 25% of patients upon autopsy, suggesting it may be underdiagnosed during life (1,2,4). The nervous system can be affected at various sites, with common central nervous system (CNS) involvement including the hypothalamus/optic chiasm and meninges. Cranial nerve involvement, especially of the facial and optic nerves, is frequent. However, area postrema involvement has not been previously reported in the neurosarcoidosis literature (5). Diagnosing sarcoidosis typically requires clinical and radiological evidence, non-caseating granulomas, and the exclusion of other conditions. A thorough evaluation for systemic involvement is essential, as illustrated by the resolution of our case with corticosteroid treatment and close follow-up.

This case report highlights area postrema syndrome as a rare and significant presentation in the context of neurosarcoidosis.

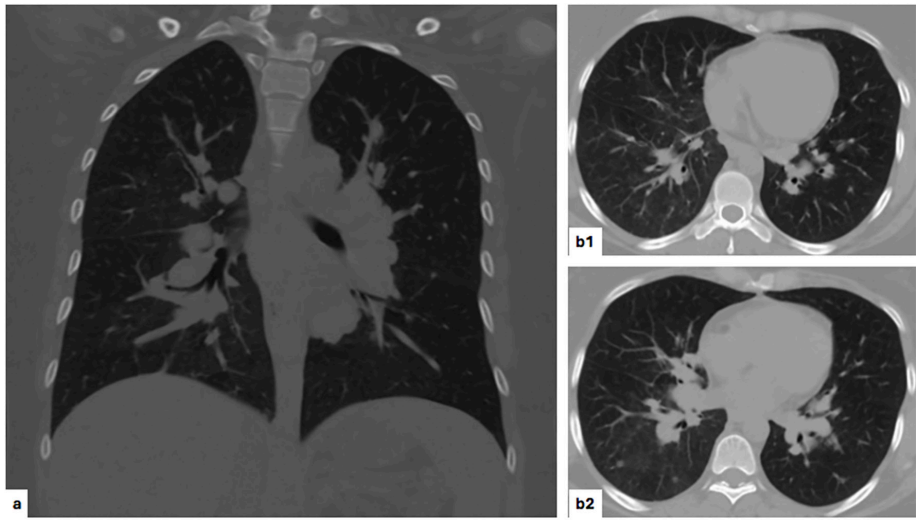

Figure 3. Coronal chest CT performed with high-resolution, thin-slice reconstructions, showing bilateral hilar and mediastinal lymphadenopathy, along with perilymphatic parenchymal nodules, consistent with systemic sarcoidosis [sagittal (a) and axial (b1, b2)]

CT: Computed tomography

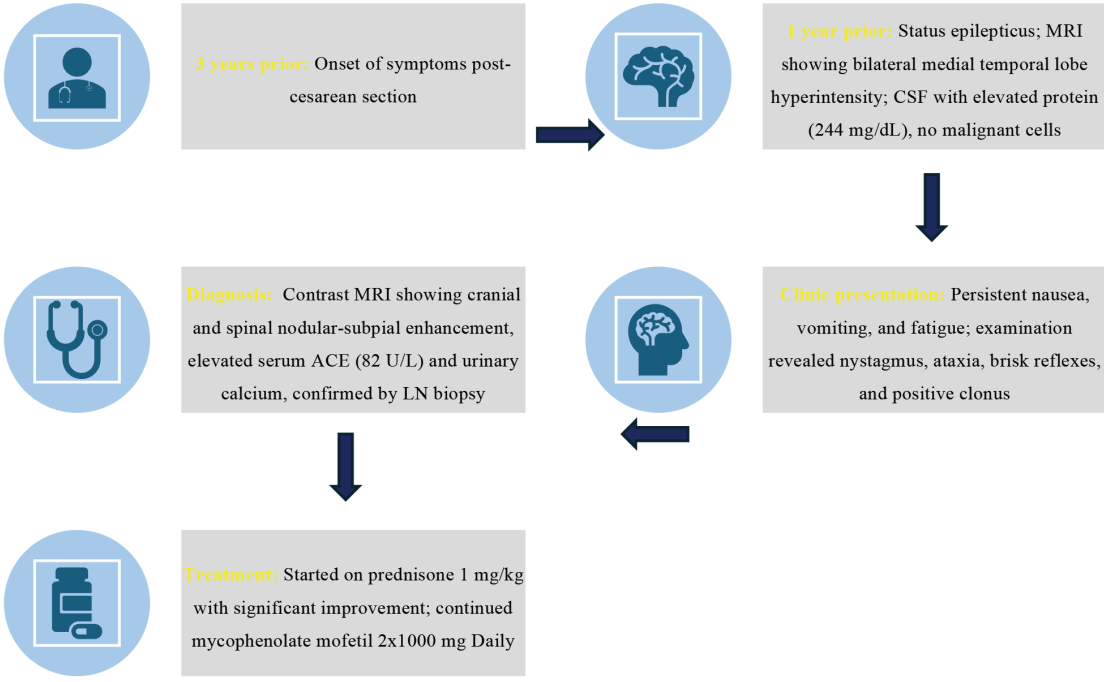

Figure 4. Neurosarcoidosis timeline. This figure provides a detailed timeline of the patient's clinical presentation, diagnostic findings, treatment interventions, and follow-up outcomes

MRI: Magnetic resonance imaging, ACE: Angiotensin-converting enzyme

The area postrema is known as a key "vomiting center", and its involvement in neuroinflammatory diseases is often associate with persistent nausea, vomiting, and hiccups.

Our findings are consistent with previous reports of neuroinflammatory diseases affecting the area postrema, such as NMOSD (1,5-7). However, this case represents an uncommon instance of neurosarcoidosis presenting with similar clinical features. MRI played a crucial role in our diagnosis, as its high sensitivity to inflammation and granulomatous changes allowed us to identify subtle but significant lesions in the brainstem and cervical spinal cord. These findings align with the those described by Stern et al. (4), emphasizing the value of advanced imaging techniques in diagnosing neurosarcoidosis. Furthermore, systemic imaging with chest CT confirmed typical sarcoidosis features, such as bilateral hilar lymphadenopathy and perilymphatic nodules. This multimodal imaging approach is essential for differentiating neurosarcoidosis from other

neuroinflammatory or demyelinating disorders (8). Recognizing area postrema syndrome in this context broadens the clinical spectrum of neurosarcoidosis and underscores the critical role of imaging in facilitating early diagnosis and treatment (9). Given the lack of randomized clinical trials in neurosarcoidosis, our findings also emphasize the importance of comprehensive diagnostic strategies that integrate both CNS and systemic evaluations.

Our case highlights the challenges of diagnosing and managing atypical presentations of neurosarcoidosis and underscores the importance of recognizing rare clinical syndromes such as area postrema syndrome. By incorporating advanced imaging techniques and systemic evaluations, we emphasize the value of a comprehensive diagnostic approach in identifying such complex cases. These findings call for increased clinical awareness and further research to improve diagnostic and therapeutic strategies in neurosarcoidosis, particularly in patients with persistent, unexplained gastrointestinal symptoms.

Ethics

Informed Consent: Informed consent was obtained.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.T., O.E., B.B., S.O., Concept: A.T., Design: A.T., Data Collection or Processing: A.T., O.E., B.B., S.O., Analysis or Interpretation: A.T., O.E., B.B., S.O., Literature Search: A.T., O.E., B.B., S.O., Writing: A.T., O.E., B.B., S.O.

Conflict of Interest: No conflict of interest was declared by the authors.

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2024 REFEREE INDEX

Abdulkadir Tunc
Arzucan Toksal Ucar
Asiye Tuba Ozdogar
Aydan Topal
Aysegul Subas
Bedriye Karaman
Bilge Piri Cinar
Burcu Altunrende
Cavid Baba
Eda Derle
Ela Simay Zengin
Erdil Arsoy
Haluk Gumus
Hasan Dogan
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Mehmet Fatih Yetkin
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Mehtap Kondak
Meral Seferoglu
Mesude Tutuncu
Nevriye Unal Suzer
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Taha Aslan
Tulin Gesoglu Demir
Turhan Kahraman
Zuhal Abasiyanik

2024 AUTHOR INDEX

2024 SUBJECT INDEX